```
     (FILE 'HOME' ENTERED AT 14:09:08 ON 05 MAR 2002)

     FILE 'MEDLINE, BIOSIS, CANCERLIT, LIFESCI, BIOTECHDS' ENTERED AT
14:09:28
     ON 05 MAR 2002
L1           399 S (CAC-1#) OR (CAC1#) OR (CAC-I#) OR (CACI#)
L2            30 S L1 AND (ENDOMETRI? OR UTER?)
L3            20 DUP REM L2 (10 DUPLICATES REMOVED)
L4         32816 S CARTER?/AU
L5           426 S L4 AND (ENDOMETRI? OR UTER?)
L6            35 S L5 AND CELL(W)LINE#
L7            29 S L6 NOT L2
L8            16 DUP REM L7 (13 DUPLICATES REMOVED)
L9         26197 S (ENDOMETRI? OR UTER?)(5A)(CELL#)
L10         3143 S L9(S)ADENOCARCINOMA#
L11        21763 S (ENDOMETRI? OR UTER?)(3A)(CELL#)
L12         2523 S L11(S)(ADENOCARCINOMA#)
L13          889 S L11(S)BLAST?
L14          368 S L11(S)((POOR? OR SLIGHT? OR LACK? OR MODERAT? OR
NEGLIGIBLE)(
L15          268 S L11(S)UNDIFFERENTIAT?
L16           62 S L11(S)PRIMITIVE
L17         1542 S L13 OR L14 OR L15 OR L16
L18            7 S L17 AND (HYPERDIPLOID OR (HYPER-DIPLOID))
L19            0 S L17 AND (CHROMOSOM?(2A)48)
L20            1 S L17 AND (TRIPLOID OR HAPLOID)
L21            8 S L20 OR L18
L22            3 DUP REM L21 (5 DUPLICATES REMOVED)
L23           22 S L17 AND ANEUPLOID#
L24           22 S L23 NOT L21
L25           10 DUP REM L24 (12 DUPLICATES REMOVED)
L26           13 S L22 OR L25

     FILE 'JAPIO' ENTERED AT 15:36:36 ON 05 MAR 2002
L27           18 S (CAC-1#) OR (CAC1#) OR (CAC-I#) OR (CACI#)
L28         1137 S (ENDOMETRI? OR UTER?)
L29           34 S L28 AND (CELL(W)LINE# OR COMPOSITION#)

=> log y
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WEST Search History

DATE: Tuesday, March 05, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=NO; OP=ADJ			
L27	l24 and 07189828$.did.	0	L27
L26	l24 and 7189828.did.	0	L26
L25	L24 and @pd=19880913	1	L25
L24	chou$[in]	2191	L24
L23	chou$[in] and mukherjee$[in]	0	L23
L22	chou$[in] and mukherjee[in]	0	L22
L21	chou$[in] and (uteroglobin)	0	L21
L20	L19 and (endometri$2 or uter$3)	9	L20
L19	carter$[in]	2815	L19
L18	carter$/in	0	L18
DB=JPAB,EPAB,DWPI; PLUR=NO; OP=ADJ			
L17	L16 and ((cell adj line$1) or (cell near composition$1))	139	L17
L16	(endometri$2 or uter$3)	6471	L16
L15	(CAC-1) or CAC1 or (CAC/1) or (CAC-I) or (CACI) or (CAC/I)	33	L15
DB=USPT; PLUR=NO; OP=ADJ			
L14	L13 and @ad<20010328	54	L14
L13	L12 or l9 or l11	54	L13
L12	L8 and ((poor$2 or slight$2 or minimal$2 or lack$3) near differentiat$3)	24	L12
L11	L8 and primitive	15	L11
L10	L and primitive	5014	L10
L9	L8 and (undifferentiated or (negligible near differentiation))	32	L9
L8	L7 and (hyperdiploid or (hyper-diploid) or aneuploid$1)	150	L8
L7	(endometri$2 or uter$3)	11966	L7
L6	L5 and ((cell adj line$1) or (cell near composition$1))	3	L6
L5	(CAC-1) or CAC1 or (CAC/1) or (CAC-I) or (CACI) or (CAC/I)	148	L5
L4	L2 and @ad<20010328	9	L4
L3	L2 AND ad<20010328	9	L3
L2	L1 same ((cell adj line$1) or composition$1)	9	L2
L1	(CAC-1$1) or CAC1$1 or (CAC/1$1) or (CAC-I$1) or (CACI$1) or (CAC/I$1)	290	L1

WEST

Generate Collection Print

L17: Entry 127 of 139 File: DWPI Sep 13, 1988

DERWENT-ACC-NO: 1988-307391
DERWENT-WEEK: 200173

TITLE: Cell lines secreting utero-globin in vitro - contg. two immortal cell lines that secrete utero-globin in vitro when stimulated by steroid hormone

INVENTOR: CHOU, J Y; MUKHERJEE, A B

PRIORITY-DATA: 1988US-0189828 (May 3, 1988)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US N7189828 N	September 13, 1988		000	

INT-CL (IPC): C12N 0/01

ABSTRACTED-PUB-NO: US 7189828A
BASIC-ABSTRACT:

Two immortal cell lines secrete uteroglobin in vitro when stimulated by a steroid hormone. The invention includes a method for screening the steroid stimulating property of a cpd..

Two immortal cell lines secrete uteroglobin in vitro when stimulated by a steroid hormone. The invention includes a method for screening the steroid stimulating property of a cpd..
ABSTRACTED-PUB-NO:

US N7189828N EQUIVALENT-ABSTRACTS:

not issued

WEST

Generate Collection Print

L14: Entry 24 of 54 File: USPT Dec 21, 1999

DOCUMENT-IDENTIFIER: US 6004528 A
TITLE: Methods of cancer diagnosis and therapy targeted against the cancer stemline

DATE FILED (1):
19970918

Brief Summary Paragraph Right (11):
It has also been noted, as mentioned, that a variety of cancer cell types can differentiate to varying degrees. For example, human neuroblastoma cells sprout axons and dendrites when grown as explants and murine leukemic cells differentiate into benign granulocytes and macrophages when grown in vitro. Moreover, tritiated thymidine labeling of rodent squamous cell carcinomas and skeletal muscle tumors illustrates that poorly differentiated cells within these tumors can give rise to well-differentiated squamous epithelia and multinucleated myotubes, respectively. In addition, somatic tissues of transplantable mouse teratocarcinomas have been shown to be benign differentiated progeny of a subpopulation of poorly differentiated embryonal carcinoma cells within these particular tumors. Most recently, all-trans-retinoic acid (ATRA) has been found to be efficacious in the treatment of human acute promyelocytic leukemia (APL) by inducing terminal differentiation of malignant leukocytes (Pierce et al (eds.), "Cancer: a problem of developmental biology", New Jersey: Prentice Hall Inc. (1978); Degos et al, "All Trans-Retinoic Acid as a Differentiating Agent in the Treatment of Acute Promyelocytic Leukemia", Blood, 85: 2643-2653 (1995)).

Detailed Description Paragraph Right (2):
Normal adult stem cells are "embryonic-like" remnants of early development which function in adult tissues as founder cells responsible for cell lineage development/tissue renewal (Potten et al, "A Comparison of Cell Replication in Bone Marrow, Testis, and Three Regions of Surface Epithelium", Biochim. Biophys. Acta, 560:281-299 (1979); Wolpert, "Stem cells: a problem in asymmetry", J. Cell Sci. Suppl., 10:1-9 (1988)). These poorly-differentiated immortal cell types reside in well-defined environmental niches localized to the basal layer of renewing tissue types including seminiferous tubules (in the case of primordial germ cells) as well as epidermis, intestinal crypts, and mammary terminal ducts among others. It is within these sequestered regions that stem cells ensure proper tissue renewal, as described independently by Potten and Wolpert, by maintaining a constant founder cell population while concomitantly replacing aged cells and in doing so creating a local microenvironment wherein maturing/differentiating progeny cells migrate away from a fixed stem cell position (Potten et al, "A Comparison of Cell Replication in Bone Marrow, Testis, and Three Regions of Surface Epithelium", Biochim. Biophys. Acta, 560:281-299 (1979); Wolpert, "Stem cells: a problem in asymmetry", J. Cell Sci. Suppl., 10:1-9 (1988)).

Detailed Description Paragraph Right (11):
Interestingly, there is evidence that stem cells are the cell type of origin for a variety of hematologic as well as solid malignancies which begs the question as to how many more alterations would be required by stem cells, which are already poorly-differentiated and "immortal", to assume a neoplastic phenotype? It had been previously described by Pierce that certain cancer cell types were no less differentiated at the histopathological level than stem cells from their corresponding lineages of origin. In addition, the renewal rates of a variety of developing tissues known to harbor stem cells (e.g., bone marrow, gastrointestinal tract, and testis) have been reported to be comparable to the exponential growth rates of corresponding cancer cell types derived from these tissues (Sell et al, "Maturation Arrest of Stem Cell Differentiation as a Common Pathway for the Cellular Origin of Teratocarcinomas and Epithelial Cancers", Lab. Invest., 70:6-22 (1994)); Pierce et al (eds.), "Cancer: a

problem of development biology", New Jersey: Prentice Hall Inc. (1978)). Based on these mentioned findings it appears that the major difference between a stem cell and a cancer cell arising from the same tissue of origin is the mode by which these two poorly-differentiated immortal cell types divide (i.e., asymmetric mitosis leading to arithmetic cellular growth vs. symmetric mitosis leading to exponential cellular growth, respectively), an epigenetically-derived trait.

Detailed Description Paragraph Right (19):
By the OSES model then the phenomenon of tumor "progression" would correspond to a gross histopathologic change due to the gradual emergence of pre-existing cancer cells rather than the stepwise selection of individual "pre-cancerous" intermediates. The preferential outgrowth of a clone(s) of cancer cells from amongst its slower-growing (i.e. differentiating/regressing) neighbors could then be attributed to the advantageous acquisition of mutations which inhibit that mutant clone's ability to differentiate. More specifically, by the OSES model peripherally-located cancer cells in a tumor mass may be the most susceptible population to selective pressure for differentiation-impairing mutations thereby effectively "shielding" the more centrally-located cancer cells of such pressures (and thus of significant mutational accumulation). Accordingly, expansion of peripherally-located mutants which are differentiation-defective (and which may or may not have a limited proliferative capability) might further shield a more centrally-located subpopulation thereby allowing it to expand and act as an "immortal" founder line (i.e. cancer stemline) that is relatively mutationally-spared. This idea is consistent with reports that certain human tumors (e.g. breast carcinomas) have a higher histopathological grade in their more central regions as well as with findings that some highly aneuploid tumor types have a chromosomal distribution pattern best accounted for by the presence of a stemline which is neareuploid (Lennington et al, "Ductal carcinoma in situ of the breast. Heterogeneity of individual lesions", Cancer, 73:118-124 (1994); Makino, "Further Evidence Favoring The Concept of the Stem Cell In Ascites Tumors Of Rats", Ann. N.Y. Acad. Sci., 63:818-830 (1956); Shapiro et al, "Isolation, Karyotype, and Clonal Growth of Heterogeneous Subpoplations of Human Malignant Gliomas", Cancer Res., 41:2349-2357 (1981)). If some mutations could affect tumor growth behavior subsequent to the birth of a cancer cell (e.g. by inhibiting cancer cell differentiation) then another potential non-neo-Darwinian explanation for an inherited cancer predisposition (in addition to predisposing to the early "initiation" stage of cancer by causing non-stem cells to aberrantly differentiate) might also derive from germline inheritance of a mutant gene that accelerates the latter "progression" stage of cancer by thwarting differentiation/reversion of cells which are already cancerous.

Detailed Description Paragraph Right (20):
It should be noted that it had been previously described by Pierce that certain malignant cell types including neuroblastoma, leukemia, rhabdomyosarcoma, and mammary adenocarcinoma are capable of "differentiating" into benign tissues. Namely, classic experiments involving thymidine labeling of rat squamous cell carcinomas and single cell cloning of murine teratocarcinomas revealed that the poorly-differentiated cells within these particular tumor types had given rise to well-differentiated tumor cells but not vice versa (i.e., not via dedifferentiation). It was further shown in these experiments that the poorly-differentiated cells within these neoplasms were the cell types responsible for tumor growth and invasion while their well-differentiated progeny had essentially lost malignant growth potential and were thus deemed to be "benign" (Pierce et al (eds.), "Cancer: a problem of development biology", New Jersey: Prentice Hall Inc. (1978)). A question not adequately addressed at the time but which may be able to be evaluated by current molecular techniques is whether the "benign" cells within these particular experimental rodent tumors are analogous to those "benign" cells normally classified as "pre-cancerous" in human tumors. In other words, as hypothesized here, cells within a "benign-appearing" region of human tumors may actually constitute differentiated progeny of pre-existing cancer cells rather than "pre-cancerous" intermediates. Re-exploration of these mentioned early experiments with current molecular biological techniques should elucidate whether rodent tumors previously shown to harbor evidence of cancer cell differentiation also possess a mutational distribution similar to that described for human neoplasms--a distribution that has been attributed to conventional mutation-selection. Detection of a similar mutational distribution should provide further evidence that the OSES model (which invokes cancer cell differentiation) provides an equivalent explanation as neo-Darwinism for the presence of "benign-appearing" cells within human cancers--and a better explanation than conventional models for cases of epigenesis in carcinogenesis (as argued previously).

Detailed Description Paragraph Right (58):

As mentioned, according to the OSES model, cancer cells are symmetrically-dividing stem cells. Therefore, certain antigens present on normal stem cells will also be present on cancer cells for "neutral" reasons (i.e. because of en bloc inheritance) rather than for reasons of "selection". In addition, antigens shared by both cancer cells and stem cells should also to some extent be present on embryonic progenitor cells from which adult stem cells are derived (due also to inheritance). Accordingly, as embryonic progenitor cells, stem cells, and cancer cells from the same tissue of origin will share certain surface antigens (which may subsequently be lost during cell differentiation and thus not readily detectable in adult tissues), identification of such shared antigens for use as potential targets for immunotherapy for cancer (i.e. to target the cancer stemline) should be sought. This can be assisted via study of embryonic or adult stem cells, for the purpose of identifying cell surface antigens present on these non-cancerous cell types, which may be technically easier to isolate and characterize than those on cancer stemline cells themselves. A proportion of such antigens would then, according to the OSES model, be presumed to be present on a cancer stemline derived from that particular tissue and thus worthy of therapeutic targeting. This method contrasts with classic immunotherapies which have not targeted native stem cell antigens but rather antigens present on highly proliferative (often mutant) cancer cells, which by the OSES model is a cell population that does not represent the immortal population which needs to be most aggressively targeted. In support of the above OSES-derived proposal that certain wildtype cell products (e.g. cell surface antigens) may be shared by embryonic cells and adult stem cells along with cancer cells from that particular tissue type, there is evidence that some tumor cell types (both of hematopoietic as well as solid origin) share expression of isoforms of certain fetal stage-specific genes including in some cases embryonic cell-surface antigens with their normal stem cell counter-parts (Sachs, "Cell Differentiation and Bypassing of Genetic Defects in the Suppression of Malignancy", Cancer Res., 47:1981-1986 (1987); Hall, "Stem Cell Is a Stem Cell Is a Stem Cell", Cell, 33:11-12, (1983); Sigal et al, "The liver as a stem cell and lineage system", Am. J. Physiol., 263:G139-G148 (1992)). For example, certain cell surface antigens (e.g. SSEA antigen family) detected on murine germ cell-derived tumors have also been detected on adult oocytes (i.e. germline stem cells) as well as on 4-8 cell mouse embryos (Hall, "Stem Cell Is a Stem Cell Is a Stem Cell", Cell, 33:11-12, (1983)). Moreover, expression of several cell surface antigens as well as other primitive gene products including alpha-fetoprotein (AFP) and IGF-2 have been detected in hepatic tumor cells, adult stem cells of the liver, as well as in fetal liver indicating shared gene expression by these temporally-distinct but related cancerous and non-cancerous cell types (Sigal et al, "The liver as a stem cell and lineage system", Am. J. Physiol., 263:G139-G148 (1992)). While conventional models might attribute such findings to dedifferentiation of an adult cell to a more primitive form, the OSES model as mentioned argues that such similarities in gene expression between cancer cells, adult stem cells, and embryonic cells is due to inheritance and not to dedifferentiation or selection. In this manner, the OSES model seems more parsimonious than conventional ones in that it need not be forced to invoke selection (as conventional models are) to explain the presence of surface antigens which appear for all intents and purposes to be "neutral" (i.e. without any selective benefit) a concept which has posed somewhat of a problem for conventional models.

Detailed Description Paragraph Right (139):
While the mammary gland is unique in that it undergoes the majority of its development ex utero, other tissue types develop mostly in utero thereby making detection of aberrant development (i.e. symmetric stem cell mitosis/cancer) in other tissue types possible prior to pubescence and conceivably possible as early as during embryogenesis. Interestingly, as mentioned previously, there are a group of independently reported enigmatic findings that a subset of patients possess shared genetic alterations (e.g. loss of heterozygosity of WT-1 or hypermethylation of H19, loss of heterozygosity of breast cancer-related loci, and micro-satellite mutator phenotype defects) in both tumorous as well as synchronous non-neoplastic tissues (Chao et al, "Genetic mosaicism in normal tissues of Wilms' tumor patients", Nature Genet., 3:127-131 (1993); Moulton et al, "Epigenetic lesions at the H19 locus in Wilms' tumor patients", Nature Genet., 7:440-447 (1994). Deng et al, "Loss of Heterozygosity in Normal Tissue Adjacent to Breast Carcinomas", Science (Washington D.C.), 274:2057-2059 (1996); Parsons et al, "Mismatch Repair Deficiency in Phenotypically Normal Human Cells", Science (Washington D.C.), 268:738-740 (1995)). These findings indicate that such genomic alterations shared by neoplastic and non-neoplastic tissues must have occurred in the common embryonic ancestor cell which gave rise to both the neoplastic cells as well as normal-appearing cells of the same tissue type. Conventional models would expect such mutation-harboring normal tissues (like their neoplastic counterparts), by virtue of their apparent possession of cancer-predisposing alterations, to display histopathological evidence of "overgrowth"--a prediction not supported by the evidence.

Such seemingly enigmatic findings, however, are consistent with the OSES model wherein such genomic alterations present in embryonic progenitor cells are passed on to adult stem cells but do not endow a selective advantage, as would be expected by conventional models, but rather predispose to aberrant differentiation of non-stem cells within a stem cell milieu thereby predisposing to subsequent symmetric stem cell mitoses. By this model, in its initial stages, symmetrically-dividing stem cells may not be histologically detectable since their cancer cell progeny are differentiating in a relatively orderly manner--however, such a lesion would be detectable by OSES-derived methods designed to detect symmetrically-dividing stem cells.

Detailed Description Paragraph Right (140):
Accordingly, early detection methods arising from the OSES model should allow assessment of a cancer prophecy at an early age, at birth, or even possibly in utero. Detecting cancer this early would of course not be possible according to the conventional cancer model which is predicated upon the notion that cancer involves a series of gradual and cumulative cellular derangements occurring after tissue morphogenesis (i.e. later in life). Of course, most tumors will not be detectable this early even by the OSES method, as most tumors will not be initiated until adulthood as a result of somatic disruption (rather than early developmental disruption) of a stem cell milieu. However, adult-onset tumors will also, for similar reasons, be detectable much earlier by OSES-derived methods than by conventional means.

L3 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1985:214708 BIOSIS
DOCUMENT NUMBER: BR29:104704
TITLE: ISCN 1985 AN INTERNATIONAL SYSTEM FOR HUMAN CYTOGENETICS NOMENCLATURE REPORT OF THE STANDING COMMITTEE ON HUMAN CYTOGENETIC NOMENCLATURE.
AUTHOR(S): **HARNDEN D G; KLINGER H P**
CORPORATE SOURCE: MANCHESTER.
SOURCE: HARNDEN, D. G. AND H. P. KLINGER (ED.). ISCN 1985: AN INTERNATIONAL SYSTEM FOR HUMAN CYTOGENETICS NOMENCLATURE: REPORT OF THE STANDING COMMITTEE ON HUMAN CYTOGENETIC NOMENCLATURE. VI+117P. S. KARGER: BASEL, SWITZERLAND; NEW YORK, N.Y., USA. ILLUS. PAPER, (1985) 0 (0), VI+117P. ISBN: 3-8055-3870-7.
DOCUMENT TYPE: Book
FILE SEGMENT: BR; OLD
LANGUAGE: English
AB This report consists of 8 chapters of interest to those using nomenclature
for human cytogenetics. After a brief historical introduction, nomenclature for normal chromosomes and constitutional chromosome aberrations are detailed. Chapters 3 and 4 discuss variable chromosome features and high resolution banding before chapters 5 and 6 give nomenclature for acquired chromosome aberration and human meiotic chromosomes. A short mention of species codes is delivered before the nomenclature and presumptive homologies for the chromosomes of the Great Apes are outlined. The text is supplemented with references, an index, 3 appendices, a karyotype fold-out, and some diagrams, tables, and micrographs. This book is published in collaboration with the March of Dimes Birth Defects Foundation and Cytogenetics and Cell Genetics.

L8 ANSWER 1 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:294821 BIOSIS
DOCUMENT NUMBER: PREV200000294821
TITLE: Retinoic acid affects the EGF-R signaling pathway during differentiation induction of human **endometrial** adenocarcinoma cells.
AUTHOR(S): **Carter, Charleata A. (1)**; Shaw, Benjamin L.
CORPORATE SOURCE: (1) Slot 518, Department of Ob/Gyn, University of Arkansas for Medical Sciences, 4301 West Markham Street, Little Rock, AR, 72205 USA
SOURCE: Experimental and Molecular Pathology, (June, 2000) Vol. 68,
No. 3, pp. 170-186. print.
ISSN: 0014-4800.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have shown that moderately differentiated **endometrial** adenocarcinoma (RL95-2) cells differentiate in response to retinoic acid treatment, illustrated by their reorganization of actin filaments and cell enlargement (Carter et al., Anticancer Res. 16, 17-24, 1996). Tyrphostin, an inhibitor of epidermal growth factor receptor (EGF-R)-associated protein tyrosine kinases, caused a dramatic reorganization of actin filaments in RL95-2 cells, similar to retinoic-acid-treated cells (Carter and Bellido, J. Cell. Physiol. 178, 320-332, 1999). We evaluated the possibility that the differentiating effects of retinoids are due to retinoic-acid-induced decreases in phosphorylation of EGF-R and changes in downstream effector proteins. Retinoic acid caused a decrease in tyrosine phosphorylation of EGF-R. Retinoic acid treatment induced a dramatic actin filament reorganization and cell enlargement. Treatment with EGF reversed this effect, because cells treated with retinoic acid followed by EGF only possessed disrupted actin aggregates and appeared small, thus resembling medium controls. Retinoic acid induced a relocalization and decrease in the amount of Shc protein, another actin-binding protein which is an adaptor protein for EGF-R signaling. In addition, retinoic acid induced a relocalization of gelsolin from the plasma membrane to the cytoplasm. Retinoic acid decreased cell detachment in detachment assays; one-half as many retinoic-acid-treated cells detached as in controls. These results are consistent with the idea that retinoic acid induces differentiation of RL95-2 cells by interfering with the EGF-R signaling pathway.

L8 ANSWER 2 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L8 ANSWER 3 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:143755 BIOSIS
DOCUMENT NUMBER: PREV199900143755
TITLE: Decrease in protein tyrosine phosphorylation is associated with F-actin reorganization by retinoic acid in human **endometrial** adenocarcinoma (RL95-2) cells.
AUTHOR(S): **Carter, Charleata A. (1)**; Bellido, Teresita
CORPORATE SOURCE: (1) Slot 518, Dep. Ob/Gyn, Univ. Arkansas Med. Sci., 4301 West Markham St., Little Rock, AR 72205 USA
SOURCE: Journal of Cellular Physiology, (March, 1999) Vol. 178, No. 3, pp. 320-332.
ISSN: 0021-9541.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Transformed cells often express elevated levels of tyrosine-phosphorylated proteins. Inhibition of protein tyrosine kinases causes reversion of malignant cells to the normal phenotype. In the present study, we evaluated the possibility that the reversion of human **endometrial** adenocarcinoma RL95-2 cells to a stationary phenotype induced by retinoic acid was associated with inhibition of tyrosine phosphorylation of cellular proteins. We found that retinoic acid decreased the levels of tyrosine-phosphorylated proteins, as assessed by immunostaining and immunoprecipitations using specific anti-phosphotyrosine antibodies. In addition, the inhibitors of tyrosine kinases herbimycin A and tyrphostin mimicked retinoic acid, inducing F-actin reorganization and increasing the size of RL95-2 cells, as determined by measurement of cell perimeters. Because focal adhesions that connect actin filaments with the plasma membrane are major sites of tyrosine phosphorylation, we further investigated whether selected focal adhesion proteins were affected by retinoic acid. We found that retinoic acid altered the localization of focal adhesion kinase. All-trans retinoic acid was effective in reducing the levels of.focal adhesion kinase and paxillin protein. Thirteen-cis retinoic acid increased the levels of vinculin protein in the cytosolic fraction of cells. These changes are consistent with actin reorganization and reversion toward a stationary phenotype induced by retinoic acid in **endometrial** adenocarcinoma RL95-2 cells. Our results indicate that the differentiating effects of retinoids on **endometrial** cells are associated with decreases in tyrosine phosphorylation and changes in the levels and distribution of focal adhesion proteins. These findings suggest that signaling pathways that involve tyrosine kinases are potential targets for drug design against **endometrial** cancer.

L8 ANSWER 4 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L8 ANSWER 4 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:5917 BIOSIS
DOCUMENT NUMBER: PREV199900005917
TITLE: Cytoskeletal reorganization induced by retinoic acid treatment of human **endometrial** adenocarcinoma (RL95-2) cells is correlated with alterations in protein kinase C-alpha.
AUTHOR(S): **Carter, Charleata A. (1)**; Parham, Groesbeck P.; Chambers, Timothy
CORPORATE SOURCE: (1) Div. Gynecol. Oncol., Dep. Obstet. Gynecol., Slot 518, Univ. Arkansas Med. Sci., Little Rock, AR 72205 USA
SOURCE: Pathobiology, (Nov.-Dec., 1998) Vol. 66, No. 6, pp. 284-292.
ISSN: 1015-2008.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have shown previously that treatment of human **endometrial** adenocarcinoma (RL95-2) cells with either 13-cis or all-trans retinoic acid results in reorganization of actin filaments, indicating reversion to a stationary phenotype. In the present study, we investigated the role of protein kinase C (PKC) in this process. Treatment of cells with PKC inhibitors (staurosporine, bisindolylmaleimide, or G66976) resulted in morphological alterations and reorganization of actin filaments similar to retinoic-acid-treated cells. For example, RL95-2 cells treated with staurosporine flattened, exhibited cell surface extensions and some actin filaments. Bisindolylmaleimide-treated cells flattened, and actin filaments reorganized similar to retinoic-acid-treated cells. RL95-2 cells treated with Go6976, which inhibits only PKCalpha, beta, and gamma, exhibited many cell surface extensions and some actin filament reorganization. We then investigated whether retinoic acid affected the subcellular localization of PKC-alpha. In control cells, PKC-alpha was mainly evident as diffuse cytoplasmic immunostaining, with a small percentage of total PKC-alpha also evident in the plasma membrane. Retinoic acid treatment dramatically altered PKC-alpha localization, since a more distinct cytoplasmic and perinuclear staining pattern was apparent. Western blot analysis confirmed these results, since the amount of cytosolic PKC-alpha increased following retinoic acid treatment. Thus, retinoic-acid induced **endometrial** differentiation may be associated with alterations in PKC-alpha localization and signaling.

L26 ANSWER 1 OF 13 MEDLINE
ACCESSION NUMBER: 96291093 MEDLINE
DOCUMENT NUMBER: 96291093 PubMed ID: 8701927
TITLE: DNA ploidy, cell cycle kinetics, and low versus high grade atypia in endometrial hyperplasia.
AUTHOR: Michael H; Kotylo P K; Mohr M; Roth L M
CORPORATE SOURCE: Department of Pathology, Indiana University, School of Medicine, Indianapolis, USA.
SOURCE: AMERICAN JOURNAL OF CLINICAL PATHOLOGY, (1996 Jul) 106 (1) 22-8.
Journal code: 3FK; 0370470. ISSN: 0002-9173.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960905

AB There have been few studies of DNA ploidy and **cell** cycle kinetics in **endometrial** hyperplasia. The authors studied archival cases of proliferative endometrium, simple, complex and atypical endometrial hyperplasia and well, moderately, and **poorly differentiated** endometrial adenocarcinoma by flow cytometry and also evaluated the significance of the degree of cytologic atypia (low versus high) in endometrial hyperplasia relative to the occurrence of carcinoma. All proliferative endometria, all types of hyperplasia and well and **moderately differentiated** carcinomas were diploid. Two-thirds of **poorly differentiated** adenocarcinomas were **aneuploid**. Neither S-phase fractions or proliferative fractions (S+G2M) could distinguish among the different types of hyperplasia or predict which hyperplasias were associated with carcinomas.

The degree of cytologic atypia in atypical hyperplasia was not predictive of the occurrence of carcinoma. **Poorly differentiated** carcinomas showed significant differences in DNA ploidy, S-phase, and proliferative fractions from endometrial hyperplasia and lower grade carcinoma. These results support the concept that there are two fundamentally different types of endometrial carcinoma.

L26 ANSWER 2 OF 13 MEDLINE

L3 ANSWER 8 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:441146 BIOSIS
DOCUMENT NUMBER: PREV200100441146
TITLE: Retinoid-induced reorganization of the actin cytoskeleton in newly characterized human **endometrial** adenocarcinoma "**CAC-1**" cells.
AUTHOR(S): Carter, Charleata A. (1)
CORPORATE SOURCE: (1) Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, 4301 W. Markham Street, Slot 518, Little Rock, AR, 72205 USA
SOURCE: Molecular Biology of the Cell, (Dec., 2000) Vol. 11, No. Supplement, pp. 100a. print.
Meeting Info.: 40th American Society for Cell Biology Annual Meeting San Francisco, CA, USA December 09-13, 2000
ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L3 ANSWER 9 OF 20 MEDLINE DUPLICATE 2

L8 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:96491 BIOSIS
DOCUMENT NUMBER: PREV199799395694
TITLE: F-actin reorganization in moderately differentiated human **endometrial** (RL95-2) cells is mediated by protein kinase C.
AUTHOR(S): **Carter, C. A.**; Tolleson, L. M.; Parham, G. P.
CORPORATE SOURCE: Dep. Obstetrics Gynecology, Div. Gynecologic Oncology, Univ. Ark. Med. Sciences, Little Rock, AR 72205 USA
SOURCE: Molecular Biology of the Cell, (1996) Vol. 7, No. SUPPL., pp. 376A.
Meeting Info.: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996
ISSN: 1059-1524.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L5 ANSWER 1 OF 3 MEDLINE on STN
ACCESSION NUMBER: 84159733 MEDLINE
DOCUMENT NUMBER: 84159733 PubMed ID: 6706226
TITLE: **KLE**: a **cell** line with defective estrogen receptor derived from undifferentiated endometrial cancer.
AUTHOR: Richardson G S; Dickersin G R; Atkins L; MacLaughlin D T; Raam S; Merk L P; Bradley F M
CONTRACT NUMBER: CA-30687 (NCI)
N01-CP-21017 (NCI)
SOURCE: GYNECOLOGIC ONCOLOGY, (1984 Feb) 17 (2) 213-30.
Journal code: 0365304. ISSN: 0090-8258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198405
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840511

AB **KLE** is a **cell** line derived from a poorly differentiated endometrial carcinoma that is aneuploid with chromosome numbers ranging from 51 to 66 and 6-8 marker chromosomes demonstrated by G banding. Tumors harvested from five of five nude mice bearing an inoculum for more than a month resemble the original specimen, and electron microscopy shows microvilli, many junctional processes, glycogenation, and a prominent nucleolonema. The cell cytosol contains a specific binder for estradiol, but there is no estrogen receptor in the nucleus and in a study reported elsewhere (Raam et al., Breast Cancer Res. Treat. 2, 277 (1982)) translocation to the nucleus fails to occur. The enzyme phenotype of this cell is human, non-HeLa.

L26 ANSWER 4 OF 13 MEDLINE
ACCESSION NUMBER: 91366216 MEDLINE
DOCUMENT NUMBER: 91366216 PubMed ID: 1890350
TITLE: Flow cytometric DNA analysis of uterine endometrial carcinoma.
AUTHOR: Izumi S; Yamaoka K; Arai H; Watanabe T; Tsutsui F; Tamura S; Nozawa S; Kurihara S
CORPORATE SOURCE: Department of Obstetrics and Gynecology, 2nd Tokyo National Hospital.
SOURCE: NIPPON SANKA FUJINKA GAKKAI ZASSHI. ACTA OBSTETRICA ET GYNAECOLOGICA JAPONICA, (1991 Jul) 43 (7) 722-8. Journal code: INR; 7505749. ISSN: 0300-9165.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911103
Last Updated on STN: 19911103
Entered Medline: 19911016

AB The DNA content in individual cells from 40 cases of histopathologically normal endometria, 15 of endometrial hyperplasia and 68 of endometrial adenocarcinoma was measured by flow cytometry. An **aneuploid** cell population was found in 50% of malignant endometria, but in the remaining endometrial carcinomas, the flow cytometrical findings showed no difference from those of benign tissue. **Aneuploidy** was more common (77.8%) in **poorly differentiated** tumors than in highly differentiated tumors (35.5%). Two and more **aneuploid** cell populations were found in 8 cases of 34. The DNA indices of **aneuploid** tumors were classified into 3 groups: hyperdiploidy, low hyperdiploidy (DNA index range: 1.04-1.2) and high hyperdiploidy (DNA index range: More than 1.2). The proportion of tumors with a high DNA index tended to increase as tumors became less differentiated. In normal **endometria** the fraction of **cells** with DNA content corresponding to the s-phase (s-fraction) was 8 +/- 3% on average in the proliferative phase. In well differentiated diploid tumors the s-fraction was 12 +/- 6%, but in moderately and **poorly differentiated** tumors it was higher (16.0% and 19.0%).

L26 ANSWER 5 OF 13 MEDLINE
ACCESSION NUMBER: 90263906 MEDLINE

L26 ANSWER 8 OF 13 MEDLINE
ACCESSION NUMBER: 86276192 MEDLINE
DOCUMENT NUMBER: 86276192 PubMed ID: 3732924
TITLE: Establishment and characterization of two human ovarian endometrioid carcinoma cell lines (with or without squamous cell component).
AUTHOR: Ishiwata I; Ishiwata C; Soma M; Ishikawa H
SOURCE: GYNECOLOGIC ONCOLOGY, (1986 Sep) 25 (1) 95-107. Journal code: FXC; 0365304. ISSN: 0090-8258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860917

AB The cell lines designated HMOA and HNOA were established from human ovarian adenoacanthoma and from a mouse graft of human ovarian **endometrioid** adenocarcinoma, respectively. These **cell** lines grew well without interruption for over 20 months. The cultured cells of both HMOA and HNOA lines were spindle, polygonal, and columnar, and showed a jigsaw puzzle-like arrangement and a piling-up tendency devoid of contact inhibition. When the HMOA cells were maintained at the confluent stage, the cells formed cysts and/or squamous metaplasia. The chromosome number of both cell lines varied widely and showed **aneuploidy**, while the modal chromosome number was stable at the diploid range. Both of these cell lines, HMOA and HNOA, were transplanted into the subcutis of BALB/c nude mice and produced well-differentiated adenoacanthoma and **poorly differentiated** **endometrioid** adenocarcinoma, respectively. HMOA **cells** were characterized as producing large amounts of CA125 (ovarian carcinoma marker), in vitro, in the cyst-forming phase. The HNOA cells, however, did not produce CA125.

L3 ANSWER 18 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 89028311 MEDLINE
DOCUMENT NUMBER: 89028311 PubMed ID: 3052807
TITLE: New monoclonal antibody, 1C5, reactive with human cervical adenocarcinoma of the **uterus**, with immunodiagnostic potential.
AUTHOR: Koizumi M; Uede T; Shijubo N; Kudo R; Hashimoto M; Kikuchi K
CORPORATE SOURCE: Department of Pathology, Sapporo Medical College, Japan.
SOURCE: CANCER RESEARCH, (1988 Nov 15) 48 (22) 6565-72.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198812
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881202

AB A murine monoclonal antibody, 1C5, was produced by fusion of spleen cells obtained from mice immunized with **CAC-1**, a human cell line of adenocarcinoma derived from **uterine** cervix, and NS/1 myeloma cells. 1C5 can be used for the staining of routine formalin-fixed and paraffin-embedded tissue sections. 1C5-defined antigen was found to have a molecular weight of 26,000. The 1C5-defined antigen was resistant to neuraminidase and trypsin treatment, but sensitive to periodate treatment, indicating that an epitope of the 1C5-defined antigen is a carbohydrate moiety. Immunohistochemical study using immunoperoxidase staining demonstrated that 1C5 reacted with 87% of adenocarcinomas of the **uterine** cervix, 39% of **endometrial** carcinomas of the **uterus**, 100% of ovarian mucinous cystadenocarcinomas, 43% of ovarian serous cystadenocarcinomas, 45% of adenocarcinomas of the colon, and 40% of gastric adenocarcinomas, thus showing the broad reactivity to adenocarcinoma cells of various origins. However, 1C5 did not show any reactivity to ectocervix epithelium, cervical intraepithelial neoplasia, or squamous cell carcinoma of the **uterine** cervix. In addition, adenocarcinoma of the **uterine** cervix exhibited strong cytoplasmic reactivity with 1C5, whereas **endometrial** carcinoma of the **uterus** showed the luminal reactivity. 1C5 also reacts with 95% ethanol-fixed malignant cells in cervical smears.

L3 ANSWER 19 OF 20 BIOSIS

L3 ANSWER 17 OF 20 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 89328031 MEDLINE
DOCUMENT NUMBER: 89328031 PubMed ID: 2474040
TITLE: The production and characterization of monoclonal antibody,
1C5, reactive with cervical adenocarcinoma of the **uterus**.
AUTHOR: Koizumi M; Uede T; Kudo R
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Sapporo Medical College.
SOURCE: NIPPON SANKA FUJINKA GAKKAI ZASSHI. ACTA OBSTETRICA ET GYNAECOLOGICA JAPONICA, (1989 May) 41 (5) 530-6.
Journal code: INR; 7505749. ISSN: 0300-9165.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890901

AB A new monoclonal antibody, 1C5, was produced by fusion of spleen cells obtained from mice immunized with **CAC-1**, a human cell line of cervical adenocarcinoma of the **uterus**, and NS-1 myeloma cell. The objectives of this study were to obtain moAb that can be used for routine histology and cytology, and to examine the histogenesis of cervical adenocarcinoma. 1. 1C5 reacted with 88% of cervical adenocarcinoma of the **uterus**, but did not react with cervical squamous cell carcinoma of the **uterus** and other squamous cell carcinoma. However, 1C5 reacted with some adenocarcinomas, such as **endometrial** carcinoma of the **uterus** and ovarial carcinoma. 2. The staining pattern by 1C5 was different, in cervical adenocarcinoma from that in **endometrial** carcinoma of the **uterus**, and also different in the endocervical type from that in the **endometrioid** type of cervical adenocarcinoma. Therefore, 1C5 is useful in distinguishing between two types of adenocarcinoma of the **uterus**. 3. 1C5 did not react with normal squamous cells or normal columnar cells of the **uterine** cervix, or with normal **endometrial** cells of the **uterus**. However, the columnar cells in a limited area of the squamocolumnar junction were strongly stained with 1C5. 4. 1C5 reacted with ethanol-fixed, and routine formalin-fixed and paraffin-embedded tissue. Thus, 1C5 may be used for clinical diagnosis. 5. 1C5 was found to be IgG1. 6. The molecular weight of the 1C5-defined antigen was 26,000 daltons, and the epitope of the 1C5-defined antigen was carbohydrate moiety. 7. We examined the histogenesis of cervical adenocarcinoma of the **uterus** by utilizing the reactivity of 1C5.(ABSTRACT TRUNCATED AT 250 WORDS)

L3 ANSWER 18 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 89028311 MEDLINE

L3 ANSWER 9 OF 20 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 1999106099 MEDLINE
DOCUMENT NUMBER: 99106099 PubMed ID: 9887247
TITLE: CA 125 is dominantly expressed by arrest of G0/G1 phase in **uterine** cervical adenocarcinoma cell line.
AUTHOR: Hayashi T; Hayakawa O; Kudo R
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Sapporo Medical University School of Medicine, Sapporo, 060, Japan.
SOURCE: GYNECOLOGIC ONCOLOGY, (1998 Dec) 71 (3) 442-9.
Journal code: FXC; 0365304. ISSN: 0090-8258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990208

AB Our purpose is to evaluate at which phase of the cell cycle CA 125 is dominantly expressed in a **uterine** cervical adenocarcinoma cell line (**CAC-1**). By a flow cytometric analysis of CA 125 expression, approximately 50% of the cells treated with interferon-gamma (IFN) were positive after 24 h. In cell cycle, the G0/G1 arrest was observed in cells treated with IFN after 24 h. The pattern for the transition of the relative rate of CA 125 expression was similar to that of the population of G0/G1. Furthermore, in the G0/G1 phase, the positive rate of CA 125 expression in cells treated with IFN was 80% of the expression in all cells after 24 h. Additionally, flow cytometry with Ki-67 demonstrated that G1 arrest occurred at 24 h, and then G0 arrest was induced by IFN after 48 h of incubation. The increased expression of CA 125 appeared mainly in the G1 phase rather than in G0.

L3 ANSWER 19 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:138533 BIOSIS
DOCUMENT NUMBER: BA87:73186
TITLE: ESTABLISHMENT AND CHARACTERIZATION OF A CELL LINE DERIVED FROM HUMAN **UTERINE** CERVICAL ADENOCARCINOMA AND ITS CHEMOSENSITIVITY TO ANTICANCER DRUGS.
AUTHOR(S): HAYAKAWA O; KUDO R; KOIZUMI M; YAMAUCHI O; YAMAMOTO H; TAKEHARA M
CORPORATE SOURCE: DEP. OBSTETRICS AND GYNECOLOGY, SAPPORO MED. COLL.
SOURCE: SAPPORO MED J, (1988) 57 (6), 603-612.
CODEN: SIZSAR. ISSN: 0036-472X.
FILE SEGMENT: BA; OLD
LANGUAGE: Japanese

AB A new cell line of a human **uterine** cervical adenocarcinoma, designated as **CAC-1**, was established from a moderately differentiated adenocarcinoma of the **uterine** cervix. **CAC -1** was subcultivated more than 150 times during 36 month period. The population doubling time was 31 hours. The number of chromosomes in the majority of cells was hypertriploidy with a mode of 75 at passage 51. In the cytoplasm, alcian blue, PAS and CEA staining positive substances could be seen. The cells produced CA-125, hCG and TPA in cultured media. The tumor obtained from nude mice inoculated with **CAC-1** cells was a moderately differentiated adenocarcinoma histologically, closely resembling the original human tumor. **CAC-1** was studied for chemosensitivity against 12 anticancer drugs by in vitro colony forming assay. In vitro sensitivity was defined as a 70% or greater inhibition of colony formation when compared to controls. Etoposide, mitomycin C and cisplatin showed sensitivity at peak plasma concentrations for 1 hour exposure. The 8 drugs, which showed sensitivity at 1/10 peak plasma concentration for 24 hour exposure, were acalcinomycin, actinomycin D, mitomycin C, etoposide, adriamycin, vincristine, vinblastine and cisplatin.

L26 ANSWER 9 OF 13 MEDLINE
ACCESSION NUMBER: 81162441 MEDLINE
DOCUMENT NUMBER: 81162441 PubMed ID: 7194144
TITLE: Histogenesis and culture of human uterine carcinosarcoma.
AUTHOR: Ishiwata I; Ishiwata C; Nagayama T; Ishikawa H
SOURCE: CANCER RESEARCH, (1981 May) 41 (5) 1978-83.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198106
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810625

AB We set out to ascertain whether uterine carcinosarcoma represents: (a) a "collision tumor," i.e., a mixture of two histogenetically distinct malignant **cell** populations (**endometrial** carcinoma and sarcoma); (b) a "combination tumor" with both histological elements of common stem cell origin; or (c) a "composition tumor," i.e., an endometrial carcinoma with reactive, atypical stroma. In in vitro cultures of human uterine carcinosarcoma, we could separate two distinct, different cell types and succeeded in establishing adenocarcinoma cell lines (HWUA-1 and HWUA-2) and sarcoma cell lines (HWUS-1, HWUS-1a, and HWUS-2). These cell lines grew well for over 10 months. HWUS-1a was hypertetraploid, HWUA-1 and HWUA-2 were pseudodiploid, and HWUS-1 and HWUS-2 were **hyperdiploid**. These cell lines were transplanted into the subcutis of BALB/c nude mice and produced tumors. HWUA-1 and HWUA-2 cell produced **poorly differentiated** adenocarcinoma, HWUS-1 and HWUS-2 produced **poorly differentiated** sarcoma, and HWUS-1a produced well-differentiated leiomyosarcoma. These results support the combination tumor theory and reject the composition tumor theory as the cause of carcinosarcoma.

L26 ANSWER 7 OF 13 MEDLINE
ACCESSION NUMBER: 88048042 MEDLINE
DOCUMENT NUMBER: 88048042 PubMed ID: 3674763
TITLE: Flow cytometric DNA analysis of normal and cancerous human endometrium and cytological-histopathological correlations.
AUTHOR: Lindahl B; Alm P; Killander D; Langstrom E; Trope C
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University Hospital, Lund, Sweden.
SOURCE: ANTICANCER RESEARCH, (1987 Jul-Aug) 7 (4B) 781-9. Journal code: 59L; 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198712
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871202

AB The DNA content in individual cells from 112 histopathologically normal endometria and from 222 malignant endometrial tumors was measured using flow cytometry. In the normal endometrial cases only single DNA peaks were found, all in the diploid region, and the range of DNA index values was used for defining the limits for diploid tumor cases. In most cases with **aneuploid** cell populations, an additional peak was found in the normal diploid region. However, combined cytological and histopathological analysis showed that a majority of these diploid cells were to be considered as tumor cells. **Aneuploid** cell populations were found in 43% of malignant endometria; in the remaining endometrial carcinomas, the flow cytometrical findings showed no differences compared to those of benign tissue. Flow cytometry in this respect did not prove useful as a diagnostic screening method. Ploidy aberrations were correlated to histopathology. **Aneuploidy** was more common (62%) in **poorly differentiated** tumors than in highly/**moderately differentiated** tumors (29%). Two or more **aneuploid** cell populations were found in 6% of the cases. No difference in **aneuploidy** was found between FIGO stage I and II (36% and 34%), but **aneuploidy** was more frequent in stage IV (86%). In normal **endometria** the fraction of **cells** with DNA content corresponding to S-phase (S-fraction) was 9.7% on average in the proliferative phase and 6.2% in the secretory phase. In well and **moderately differentiated** diploid tumors the S-fraction was about the same (8.8% and 9.2%), but in **poorly differentiated** tumors it was significantly higher (12-16.5%).

L26 ANSWER 8 OF 13 MEDLINE

L26 ANSWER 6 OF 13 MEDLINE
ACCESSION NUMBER: 88164805 MEDLINE
DOCUMENT NUMBER: 88164805 PubMed ID: 3349465
TITLE: UM-EC-1, a new hypodiploid human cell line derived from a poorly differentiated endometrial cancer.
AUTHOR: Grenman S E; Van Dyke D L; Worsham M J; del Rosario F; Roberts J A; McClatchey K D; Schwartz D R; Babu V R; Carey T E
CORPORATE SOURCE: Department of Otolaryngology/Head and Neck Surgery, University of Michigan, Ann Arbor 48109.
CONTRACT NUMBER: CA 28564 (NCI)
SOURCE: CANCER RESEARCH, (1988 Apr 1) 48 (7) 1864-73.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198804
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880422

AB The University of Michigan **endometrial** carcinoma **cell** line UM-EC-1 was derived from a **poorly differentiated** endometrial adenocarcinoma of a 66-yr-old white female. Cell cultures were started using both tumor explants and a cell suspension obtained from collagenase-treated tumor tissue. The collagenase-derived cell suspension gave rise to monolayer cultures which grew rapidly from the outset. This subline of UM-EC-1 has now been subcultured more than 50 times. Cells derived from the tumor explants grew more slowly initially, but after a lag phase of 5 to 6 wk, this subline also exhibited rapid logarithmic growth and reached the same growth rate as that of the collagenase-treated cells. The explant subline has been subcultured more than 37 times. The doubling time of both sublines is 24 h under optimal growth conditions. The karyotype of both cell cultures is 43, XX, inv(1)(p32q42), -4, +der(8) t(8;12)(p23.1;q22), del(9)(q11), -13, -13, +t(13;13) (p13;p13), del(18)(q), -19, -22, -22, +t(22;22)(p11;p11). The net result of the chromosome losses and rearrangements was monosomy 4, duplication 8p23.1----qter, deletion 9q11----9qter, duplication 12q22----qter, deletion 18q, and monosomy 19. The t(13;13) and the t(22;22) were dicentric by C-banding. Virtually all of the chromosome changes were stable in multiple passages except that there was mosaicism for chromosome 13. Some cells contained a single copy of 13 and others had t(13;13). The available evidence indicates the t(13;13) is an isochromosome. UM-EC-1 cells produced tumors histologically similar to the original tumor in male, female, and ovariectomized female athymic mice. UM-EC-1 cells express human class I histocompatibility antigens as assessed by binding of antibodies to nonpolymorphic HLA and beta-2-microglobulin antigens. Blood group antigens A and H were absent although the patient is blood type A and these antigens are normally expressed in endometrial glands. A rearrangement involving the region of chromosome nine that carries the ABH locus may be related to the absence of blood group antigen expression by these cells. The E7 membrane antigen, the locus for which resides on the

short arm of chromosome 11, was expressed strongly which is consistent with the presence of two intact copies of chromosome 11 in these cells.

L26 ANSWER 7 OF 13 MEDLINE

L26 ANSWER 5 OF 13 MEDLINE
ACCESSION NUMBER: 90263906 MEDLINE
DOCUMENT NUMBER: 90263906 PubMed ID: 2344964
TITLE: Establishment and characterization of UM-EC-2, a tamoxifen-sensitive, estrogen receptor-negative human endometrial carcinoma cell line.
AUTHOR: Grenman S E; Worsham M J; Van Dyke D L; England B; McClatchey K D; Babu V R; Roberts J A; Maenpaa J; Carey T E
CORPORATE SOURCE: Department of Otolaryngology/Head and Neck Surgery, University of Michigan, Ann Arbor 48109-0506.
CONTRACT NUMBER: 28564 (NIDA)
RCDA 00621
SOURCE: GYNECOLOGIC ONCOLOGY, (1990 May) 37 (2) 188-99.
Journal code: FXC; 0365304. ISSN: 0090-8258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 19900810
Last Updated on STN: 20000303
Entered Medline: 19900702

AB UM-EC-2 was established from a patient with **poorly differentiated** stage IB **endometrial** carcinoma. This **cell** line produces tumors in nude mice that have the same histological features as the patient's tumor. UM-EC-2 cells express b2-microglobulin, the epidermal growth factor receptor (EGF), and the H blood group antigen. This membrane antigen phenotype is consistent with **cells** of human **endometrial** origin. The karyotype of UM-EC-2 is fairly complex, with rearrangements affecting all chromosomes except 3, 10, 14, 19, and 20. There were two populations of cells, a **hyperdiploid** population with a modal number of 53-55 and a hypertetraploid population with a modal number of 109. A postulated sequence of events before and after tetraploidization is suggested based on the number of copies of individual chromosomes and rearrangements. Comparison of the UM-EC-2 karyotype to that of UM-EC-1 (a previously described line from a different patient with endometrial carcinoma) revealed that the two lines share eight very similar chromosome changes, which include loss of most of chromosome 4, breakpoints affecting proximal bands on 8p, loss of most of 9q, a breakpoint at 12q22, loss of 13q, breakpoints in proximal bands on 18q, and a breakpoint at 22p11. These changes may represent nonrandom chromosome abnormalities in **poorly differentiated** endometrial cancer. Estrogen (ER) and progesterone (PgR) receptors were not detected in either the primary tumor or the cell line. Nevertheless, UM-EC-2 cells were very sensitive to growth inhibition by tamoxifen (TAM) in vitro. One micromolar TAM caused 50% inhibition of cell growth, 2.5 microM caused cytostasis, and 5 microM TAM was cytotoxic, killing all cells after 5-7 days of exposure to the drug. Paradoxically, 100 nM estradiol (E2) caused a moderate increase in the growth of the cells but it did not prevent or reverse growth inhibitory effects of TAM. These findings support the concept that in some tumors TAM causes growth inhibition by an ER-independent mechanism. UM-EC-2 cells were also sensitive to growth regulation by EGF. Thus, these cells provide a new in

vitro model of human endometrial cancer in which the roles of both TAM and EGF as growth regulatory substances can be investigated.

L26 ANSWER 3 OF 13 MEDLINE
ACCESSION NUMBER: 92307512 MEDLINE
DOCUMENT NUMBER: 92307512 PubMed ID: 1612503
TITLE: Characterization of a human endometrial carcinoma cell line producing intraperitoneal tumor growth in immunodeficient mice.
AUTHOR: Rubin S C; Federici M G; Lloyd K O; Lewis J L Jr; Hoskins W J
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, New York 10021.
SOURCE: GYNECOLOGIC ONCOLOGY, (1992 Jun) 45 (3) 273-8.
Journal code: FXC; 0365304. ISSN: 0090-8258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920807
Last Updated on STN: 19970203
Entered Medline: 19920724

AB Establishment of laboratory models of gynecologic neoplasms provides an important means of studying the biologic characteristics of these tumors. We report a previously uncharacterized human **endometrial** adenocarcinoma **cell** line that produces both intraperitoneal and subcutaneous growth in nude mice. The line was derived from a **poorly differentiated** endometrial cancer and has been carried in continuous tissue culture for greater than 100 passages. Doubling time in culture is approximately 48 hr. Antigenic phenotyping against a panel of murine monoclonal antibodies by rosetting cell surface assay on live cells or peroxidase assay on fixed cells has shown reactivity with a number of determinants, including MH99, MT334, MQ49, and the blood group antigens F3, 118, and 41-83. Cytogenetically, the line displays an **aneuploid** human karyotype with several chromosomal rearrangements and deletions. When injected intraperitoneally into nude mice, animals develop intraperitoneal nodules and ascites and succumb with wasting in 30-40 days. The intraperitoneal tumor has been passaged multiple times in nude mice by direct transfer of ascites. Subcutaneous injection of tumor cells produces nodules that grow at a reproducible rate. By light and electron microscopy, the nude mouse tumor is a **poorly differentiated** adenocarcinoma, similar to the original patient's tumor. It expresses both estrogen and progesterone receptors. CA 125 is not elevated in the serum of animals with tumor implants. The line appears to be cisplatin sensitive as determined by rates of growth of subcutaneous nodules. This cell line may be useful in studying the in vitro and in vivo properties of human endometrial carcinoma.

L26 ANSWER 4 OF 13 MEDLINE

L8 ANSWER 8 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:52081 BIOSIS
DOCUMENT NUMBER: PREV199800052081
TITLE: Tamoxifen alters the localization of F-actin and alpha5/beta1-integrin fibronectin receptors in human **endometrial** stromal cells and carcinoma cells.
AUTHOR(S): Albright, Craig D. (1); **Carter, Charleata A.**; Kaufman, David G.
CORPORATE SOURCE: (1) Dep. Nutr., CB No. 7400 McGavran-Greenberg, Univ. N.C., Chapel Hill, NC 27599-7400 USA
SOURCE: Pathobiology, (July-Aug., 1997) Vol. 65, No. 4, pp. 177-183.
ISSN: 1015-2008.
DOCUMENT TYPE: Article
LANGUAGE: English

AB We have investigated F-actin and the integrin fibronectin receptor as possible targets of tamoxifen (TAM) signaling in a cell-based model of the **endometrium**. Normal human **endometrial** stromal cells and RL95-2 human **endometrial** adenocarcinoma cells were treated for 1 h with TAM, a known antagonist of protein kinase C (PKC), or with staurosporine or HA1004, two broad-spectrum protein kinase antagonists capable of inhibiting PKC and PKA, respectively. We utilized fluorescein-phalloidin and confocal microscopy to visualize the cellular distribution of F-actin. Normal stromal cells and RL95-2 cells differed in the arrangement of F-actin in control cells and in their response to TAM. In control stromal cells, actin stress fibers were well organized throughout the cell, but in RL95-2 cells, they were disorganized and present mainly at the cell periphery. F-actin in RL95-2 cells treated with TAM (0.1 and 1.0 muM) or with staurosporine (0.7 and 7.0 nM) exhibited a reorganization into stress fibers consistent with a more stationary phenotype. In contrast, TAM-or staurosporine-treated normal stromal cells exhibited an increase in the amount of organized F-actin. Interestingly, in normal stromal cells treated with staurosporine but not TAM or HA 1004, these F-actin fibers appeared to terminate in dense plaques proximal to the plasma membrane. The alpha5/beta1 integrin fibronectin receptor mediates between the extracellular matrix and the actin cytoskeleton. TAM induced clustering of the fibronectin receptor at the plasma membrane in normal stromal cells, but not in carcinoma cells. This study supports the importance of plasma membrane-cytoskeletal protein interactions in the response of normal and carcinoma cells to TAM.

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L8 ANSWER 5 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:394495 BIOSIS
DOCUMENT NUMBER: PREV199799693698
TITLE: State of differentiation affects the response of **endometrial** adenocarcinoma cells to retinoic acid.
AUTHOR(S): **Carter, Charleata A. (1)**; Parham, Groesbeck P.
CORPORATE SOURCE: (1) Dep. Obstetrics Gynecol., Slot 518, Univ. Arkansas Med.
Sci., Little Rock, AR 72205 USA
SOURCE: Anticancer Research, (1997) Vol. 17, No. 3C, pp. 1973-1983.
ISSN: 0250-7005.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Background: Patients with poorly differentiated **endometrial** cancers have a worse prognosis than patients with well-differentiated **endometrial** cancers. If poorly differentiated, cells in **endometrial** cancers could be induced to differentiate, they would be more responsive to hormonal manipulation, and survival rates would be increased We set up an in vitro model system to examine the effects of retinoic acid on human **endometrial** adenocarcinoma cells at three states of differentiation. Methods: Cells were treated with pharmacological doses of 13-cis or all-trans retinoic acid (0.5 mu-M, 1 mu-M or 5 mu-M), and stained for mucins or actin filaments. Results: Untreated undifferentiated (KLE) cells lack organized actin filaments and cytoplasmic mucins. Treatment with 5 mu-M retinoic acid caused some reorganization of actin filaments, but cytoplasmic mucins remained absent.
Moderately differentiated (RL95-2) cells differentiated the most with retinoic acid treatment evidenced by a dramatic reorganization of actin filaments and an increase in cytoplasmic mucins. Untreated or treated well
differentiated (Ishikawa) cells possessed well organized actin filaments and exhibit positive staining for cytoplasmic mucins. Conclusion: Retinoic
acid causes cellular differentiation in less differentiated human **endometrial** adenocarcinoma cells.

L26 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1982:260887 BIOSIS
DOCUMENT NUMBER: BA74:33367
TITLE: A NEW HUMAN CELL LINE DERIVED FROM A POORLY DIFFERENTIATED ENDOMETRIAL ADENO CARCINOMA.
AUTHOR(S): GAL D; FORNEY J P; DEV V G; PORTER J C
CORPORATE SOURCE: DEP. OF OBSTETRICS AND GYNECOLOGY, UNIV. OF TEX. HEALTH SCI. CENTER AT DALLAS, 5323 HARRY HINES BLVD., DALLAS, TEX.
75235.
SOURCE: GYNECOL ONCOL, (1982) 13 (1), 50-57.
CODEN: GYNOA3. ISSN: 0090-8258.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Establishment and characterization of an **endometrial** adenocarcinoma **cell** line are described. The tumor cells, designated AC-258, originated from a patient with a **poorly differentiated** adenocarcinoma of the **endometrium**. These **cells** have been passed in culture more than 102 times and have maintained their morphological and chromosomal integrity in a fashion suggestive of monocloning. Cells from passages 1, 58 and 102 were **aneuploid**. The average number of chromosomes per cell was 64.8 and 8-17 marker chromosomes per cell were identified and described. Histological evaluation of tumor explants from 3 passages grown in nude (athymic) mice revealed morphologic identity. The doubling time of AC-258 was 22 h. No detectable estrogen- or progesterone-binding proteins were found. The AC-258 cell line provides researchers with another tool with which to investigate biochemical and biological properties of human cancer cells.

L26 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:199746 BIOSIS
DOCUMENT NUMBER: BA89:106417
TITLE: BIOLOGICAL CHARACTERISTICS OF ADENOCARCINOMA CELL LINE HOUA-I AND B-LYMPHOBLASTOID CELL LINE HOUA-II ESTABLISHED FROM THE SAME TISSUE OF ENDOMETRIAL ADENOCARCINOMA.
AUTHOR(S): ISHIWATA I; SOMA M; ONO I; NAKAGUCHI T; ISHIWATA C; NOZAWA S; ISHIKAWA H
CORPORATE SOURCE: DEP. ANAT., JIKEI UNIV. SCH. MED., 3-25-8, NISHI-SHINBASHI, MINATO-KU, TOKYO 105, JPN.
SOURCE: JIKEIKAI MED J, (1989) 36 (4), 303-316.
CODEN: JMEJAS. ISSN: 0021-6968.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Human endometrial adenocarcinoma was cultured and **endometrial** adenocarcinoma **cell** line (HOUA-I) and B-lymphoblastoid cell line (HOUA-II) were established. HOUA-I line consists of cells of spindle-like, roundish, and polygonal shapes, arranged in epithelial pavement and proliferating in multilayers. Their doubling time is about 50 hours and plating efficiency is about 25%. The chromosomes show a wide **aneuploid** distribution, with a mode at 46, and no karyological abnormality. The cells can be transplanted on hamster and nude mouse to form **poorly differentiated** adenocarcinoma. The HOUA-I line was determined as the **endometrial** adenocarcinoma **cell** line. On the other hand, HOUA-II line consists of small roundish cells with cytoplasmic processes, and the cells proliferate as floating spherical aggregates of cells. Their doubling time is 60 hours, and the chromosomes of the stem cells are 46,XX,inv (20p+q-). They give positive results for Epstein-Barr virus nuclear antigen (EBNA) but negative result for EB-viral capsid antigen (EBVCA). Synthesis of immunoglobulin G (IgG) and c-myc gene amplification were recognized. The HOUA-II line was determined as B-lymphoblastoid cell line.

L26 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L3 ANSWER 16 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1991:504047 BIOSIS
DOCUMENT NUMBER: BA92:127007
TITLE: ANTITUMOR EFFECTS OF HUMAN RECOMBINANT INTERFERON-GAMMA AND TUMOR NECROSIS FACTOR ON FIVE CERVICAL ADENOCARCINOMA CELL LINES IN-VIVO AND IN-VITRO.
AUTHOR(S): IWASAKA T; HARA K; HAYASHI Y; YOKOYAMA M; HACHISUGA T; FUKUDA K; OKUMA Y; SUGIMORI H
CORPORATE SOURCE: DEP. OBSTET. GYNECOL., SAGA MED. SCH., SAGA 849, JPN.
SOURCE: GYNECOL ONCOL, (1991) 42 (1), 39-43.
CODEN: GYNOA3. ISSN: 0090-8258.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB We examined the antitumor effects of recombinant interferon-.gamma. (IFN-.gamma.) and tumor necrosis factor (TNF) on cervical adenocarcinoma cell lines, in vitro and in vivo. Four of five cell lines showed a high sensitivity to IFN-.gamma., in vitro. One of five cell lines showed a remarkable sensitivity to TNF, in vitro. Only one cell line resistant to both IFN and TNF was derived from a well-differentiated adenocarcinoma of endocervical type. Experiments using nude mice bearing transplanted tumors revealed that these cytokines were also effective against tumors in vivo. All these observations suggest that IFN-.gamma. or TNF can have positive effects in the treatment of patients with adenocarcinoma of the **uterine** cervix.

L3 ANSWER 17 OF 20 MEDLINE DUPLICATE 4

L3 ANSWER 14 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:174512 BIOSIS
DOCUMENT NUMBER: PREV199598188812
TITLE: Aromatase activity of human gynecological carcinoma cell lines.
AUTHOR(S): Tada, Akio (1); Nakamura, Junji; Sasaki, Hiroshi
CORPORATE SOURCE: (1) Dep. Obstet. Gynecol., Jikei Univ. Sch. Med., 3-25-8 Nishi-Shinbashi, Minato-ku, Tokyo 105 Japan
SOURCE: Jikeikai Medical Journal, (1994) Vol. 41, No. 4, pp. 407-415.
ISSN: 0021-6968.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Human cancer cell lines derived from **endometrium** (HEC-59, HHUA, Ishikawa, OMC-2), **uterine** cervix (**CAC-1**, OMC-4), ovary (2780,2008, HRA), and breast (MCF-7) were examined for aromatase activity and the effect of estradiol and testosterone on DNA synthesis. Aromatase activity was high (more than 500 fmol/10-7 cells/24 hrs) in the cell lines OMC-2 and MCF-7, moderate (100-499 fmol/10-7 cells/24 hrs) in OMC-4, HRA, HEC-59, Ishikawa, and **CAC-1**, and low (less than 100 fmol/10-7 cells/24 hrs) in HHUA, A2780, and 2008.

A significant stimulation of DNA synthesis (250% increase of (3H)-thymidine uptake) by estradiol (10-9 M) was observed in HEC-59, OMC-2, MCF-7, Ishikawa, and HRA. Stimulation of DNA synthesis by estradiol was moderate (115-249%) in OMC-4. Estradiol-dependent increase of DNA synthesis was not observed in HHUA, **CAC-1**, 2008, and A2780. The cell lines which showed the estradiol dependency in DNA synthesis, namely HEC-59, OMC-2, MCF-7, Ishikawa, and HRA, also presented testosterone dependency. These data suggest that some gynecological carcinomas may possess aromatase-dependent growth stimulation system.

L3 ANSWER 15 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:136384 BIOSIS

L3 ANSWER 13 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:412531 BIOSIS
DOCUMENT NUMBER: PREV199598426831
TITLE: Effects of single and combined application of anti-cancer drugs on cervical adenocarcinoma: I. Antitumor activity in vitro.
AUTHOR(S): Hara, K.; Iwasaka, T. (1); Matsuo, N.; Nakao, Y.; Yokoyama, M.; Yamasaki, F.; Mvula, M.; Sugimori, H.
CORPORATE SOURCE: (1) Dep. Obstet. Gynecol., Saga Med. Sch., 1-1, 5-chome, Nabeshima, Saga 849 Japan
SOURCE: Acta Obstetricia et Gynecologica Scandinavica, (1995) Vol. 74, No. 5, pp. 330-335.
ISSN: 0001-6349.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Background: Establishment of effective combination chemotherapy regimen for patients with an adenocarcinoma of the **uterine** cervix has been long-awaited because there has been no documentation concerning chemosensitivity of this tumor against conventional antitumor agents. Methods: To search for an effective combination regimen, 15 conventional antitumor drugs were tested for growth inhibitory effects on five different cervical adenocarcinoma cell lines. Results: Etoposide, mitomycin C, adriamycin, epirubicin, and vinblastine, were singularly effective. Effects of combination chemotherapy were also tested using the above five antitumor agents plus interferon-gamma. Etoposide, mitomycin C, and interferon-gamma were the most effective when given in combination. Conclusions: Combined treatment with the above three drugs seems worthy of consideration for clinical application.

L3 ANSWER 12 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:252532 BIOSIS
DOCUMENT NUMBER: PREV199799551735
TITLE: Experimental and clinical study on chemotherapy for cervical adenocarcinoma.
AUTHOR(S): Takehara, Masaki
CORPORATE SOURCE: Dep. OB/GYN, Sapporo Med. Univ. Sch. Med., Sapporo Japan
SOURCE: Sapporo Medical Journal, (1996) Vol. 65, No. 5, pp. 433-444.
ISSN: 0036-472X.
DOCUMENT TYPE: Article; (THESIS/DISSERTATION)
LANGUAGE: English
SUMMARY LANGUAGE: English; Japanese

AB We examined the chemosensitivity of adenocarcinoma of the cervix in advanced, recurrent and high risk patients. First, we studied chemosensitivity against 12 anticancer drugs by in vitro colony forming assay using 4 cervical adenocarcinoma cell lines. Those lines were OMC-4 (well differentiated), **CAC-1** (moderately differentiated), TMCC-1 (poorly differentiated) and JSK- 1 (**endometrioid** type). In vitro sensitivity was defined as a 70% or greater inhibition of colony formation when compared to controls. The 4 drugs which showed effectivity in all cell lines were VP-16, ACM, ADM, ACD. MMC showed high effectivity in the 3 lines of endocervical adenocarcinoma. CDDP showed it in only **CAC-1**. Next, we examined the effectiveness of the 5 anticancer drugs MMC, CDDP, ACM, ACD and VP-16 in nude mice transplanted with the above 4 lines of adenocarcinoma. The therapeutic effects were assessed in terms of growth inhibition rates and histological effects in the transplanted tumors of nude mice. The following results were obtained: In single drug administration, MMC was effective in all tumors, and CDDP was effective in 3 kinds of tumors in terms of growth inhibition. Histological findings under the drugs did not correlate with therapeutic findings. In combined administration, MMC+CDDP was the most effective in terms of growth inhibition; this combination showed an additive effect, and MMC and CDDP were concluded to be key drugs for treating cervical adenocarcinoma. On the basis of these results, we used combination therapy with CDDP, ACM and MMC (here termed PAM) against cervical adenocarcinoma in 9 patients with advanced or recurrent adenocarcinoma of the **uterine** cervix. This regimen was administered intravenously or intraarterially. In intravenous infusion, it consisted of CDDP 70 mg/m-2 and ACM 30 mg/m-2 on Days 1 and MMC 5 mg/ m-2 on Days 2 and 3. In intraarterious infusion, CDDP 70 mg/m-2, ACM 30 mg/m-2 and MMC 10 mg/m-2 were given in one shot or over a series of some days, every 4 weeks. The overall response rate was 66.7%. This included one complete (CR) and five partial (PR) responses. The patient showing CR has survived for 7.5 years since adjuvant irradiation therapy. The 5 PR patients improved enough to be operable, and 3 have survived for 1 year apprx 2 years. The toxicities of this regimen were not significant.
Chemotherapy by this regimen seems to improve the prognosis of advanced, recurrent or high risk patients following radical surgery or irradiation therapy.

L3 ANSWER 11 OF 20 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 1998016642 MEDLINE
DOCUMENT NUMBER: 98016642 PubMed ID: 9355022
TITLE: Inhibitory effects of ubenimex (bestatin) on the invasion of **uterine** cervical carcinoma cells and their production and activation of gelatinase A.
AUTHOR: Ueda M; Ueki M; Fujii H; Yoshizawa K; Nakajima M
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Osaka Medical College, Japan.
SOURCE: JOURNAL OF MEDICINE, (1997) 28 (3-4) 175-90.
Journal code: IYG; 7505566. ISSN: 0025-7850.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971204

AB The present study was undertaken to investigate the effects of the aminopeptidase inhibitor ubenimex (bestatin) on the invasive activity of cultured human **uterine** cervical carcinoma cells. The invasion of squamous cell carcinoma OMC-1 and SKG-IIIb cells, and adenocarcinoma OMC-4 and **CAC-1** cells into reconstituted basement membrane (Matrigel) was inhibited by the presence of bestatin in a concentration-dependent manner. However, bestatin did not have any effect on tumor cell proliferation or migration. Immunoblot analysis of tumor-conditioned medium showed that the treatment of tumor cells with bestatin resulted in the reduction of the 72 kDa gelatinase level (gelatinase A, latent form) in the four cell lines examined, and the reduction of the 68 kDa gelatinase level (gelatinase A, active form) in SKG-IIIb cells. Bestatin inhibited hydrolyzing activities towards substrates of aminopeptidases in tumor cells, but did not directly inhibit gelatinase A. These results suggest that bestatin may inhibit the invasion of **uterine** cervical carcinoma cells possibly through the inhibitory mechanisms for production and activation of gelatinase A modulated by tumor aminopeptidases.

L3 ANSWER 7 OF 20 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001080827 MEDLINE
DOCUMENT NUMBER: 20567591 PubMed ID: 11115359
TITLE: A newly characterized human **endometrial** adenocarcinoma cell line (**CAC-1**) differentiates in response to retinoic acid treatment.
AUTHOR: Carter C A; Madden V J
CORPORATE SOURCE: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.. charleatacarter@yahoo.com
SOURCE: EXPERIMENTAL AND MOLECULAR PATHOLOGY, (2000 Dec) 69 (3) 175-91.
Journal code: EQ5. ISSN: 0014-4800.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

AB A new cell line of poorly differentiated human **endometrial** adenocarcinoma cells termed "**CAC-1**" cells has been established. These cells are epithelial, as indicated by positive cytokeratin and negative vimentin staining. They are rounded and possess a high nuclear-to-cytoplasmic ratio, desmosomes, surface microvilli, intercelular lumens, and pleomorphic nuclei containing multiple nucleoli. These cells have been in long-term culture for 2 years. Our previous studies demonstrated that moderately differentiated (RL95-2) cells differentiated in response to retinoic acid treatment, illustrated by their reorganization of actin filaments and cell enlargement (Carter et al., 1996; Anticancer Res. 16, 17-24). **CAC-1** cells exhibited a similar response because they also organized actin filaments and enlarged in response to retinoic acid treatment. Concurrently, retinoic acid treatment caused a 40% decrease in cell detachment in an in vitro detachment assay compared to controls. A slight lag in cell growth was observed when **CAC-1** cells were treated with 1 microM 13-cis or all-trans retinoic acid during a 12-day growth curve. In addition, we examined the effects of retinoic acid on protein kinase C-alpha (PKC-alpha) and myristoylated alanine-rich C-kinase substrate (MARCKS). Treatment with retinoic acid caused cytoplasmic PKC-alpha to increase concomitant with a decrease in PKC-alpha in the membrane. In contrast, MARCKS increased in the membrane in response to retinoic acid treatment. These data indicate that retinoid treatment causes inactivation of PKC-alpha, allowing MARCKS to relocalize to the membrane, where it can cross-link actin filaments. **CAC-1** cells represent an ideal model for investigating the effects of retinoids on differentiation induction concomitant with actin reorganization.

L3 ANSWER 8 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L3 ANSWER 2 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:160271 BIOSIS
DOCUMENT NUMBER: PREV200100160271
TITLE: Correlation between thymidine phosphorylase expression and invasion phenotype in cervical carcinoma cells.
AUTHOR(S): Ueda, Masatsugu (1); Terai, Yoshito; Kumagai, Koji; Ueki, Ken; Kanemura, Masanori; Ueki, Minoru
CORPORATE SOURCE: (1) Department of Obstetrics and Gynecology, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka, 569-8686: gyn017@poh.osaka-med.ac.jp Japan
SOURCE: International Journal of Cancer, (15 March, 2001) Vol. 91, No. 6, pp. 778-782. print.
ISSN: 0020-7136.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The correlation between thymidine phosphorylase (dThdPase) expression and invasion phenotype in human **uterine** cervical carcinoma cells was investigated using 10 cervical carcinoma cell lines. Semi-quantitative reverse transcription-polymerase chain reaction analysis was performed to investigate the mRNA levels of dThdPase and matrix metalloproteinase (MMP)-2 with beta-actin coamplified as an internal standard. dThdPase protein expression levels were detected by highly sensitive enzyme-linked immunosorbent assay. Tumor cell migration along a gradient of substratum-bound fibronectin and invasion into reconstituted basement membrane were evaluated by haptotactic migration and invasion assay. Although dThdPase mRNA and protein expression levels differed remarkably among the cell lines, there was a statistical correlation between them ($r = 0.743$, $p = 0.0139$). dThdPase gene and protein expression levels were well correlated with the number of cells that migrated and invaded ($p < 0.05$). Moreover, there was a close correlation between MMP-2 gene and dThdPase gene and protein expression levels ($p < 0.05$). Tumor cells that produce dThdPase may have a higher invasive and metastatic potential because of their capacity to pass through tissue barriers.

L3 ANSWER 3 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L8 ANSWER 12 OF 16 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 92181589 MEDLINE
DOCUMENT NUMBER: 92181589 PubMed ID: 1543549
TITLE: Effects of the SV40 large T antigen and EJ ras oncogene on fibronectin localization in human **endometrial** cells as viewed by confocal laser scanning microscopy.
AUTHOR: **Carter C A**; Vollmer G; Kaufman D G
CORPORATE SOURCE: Experimental Carcinogenesis and Mutagenesis Branch, National Institute of Environmental Health Sciences, Research Triangle Park, N.C. 27709.
CONTRACT NUMBER: CA31733 (NCI)
ES07017 (NIEHS)
SOURCE: PATHOBIOLOGY, (1992) 60 (1) 33-41.
Journal code: AF6; 9007504. ISSN: 1015-2008.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 19920424
Entered Medline: 19920413

AB We utilized confocal laser scanning microscopy to examine the localization of fibronectin deposition in cultures of human **endometrial** stromal cells. We found that fibronectin in normal human **endometrial** stromal cell cultures was both intracellular, occurring in rough endoplasmic reticulum and in perinuclear regions, and extracellular, occurring diffusely over the entire cell surface. **Endometrial** stromal cells were transfected with a plasmid containing an origin-defective Simian Virus 40 (SV40) which codes for a temperature-sensitive large T antigen. When these cells were placed under temperature-restrictive conditions for large T-antigen function, they exhibited staining patterns similar to normal **endometrial** cells. Fibronectin deposition in cultures of partially or fully transformed **endometrial** cells was not intracellular as in normal cells, but was localized primarily between cells. Cells expressing the SV40 large T antigen deposited fibronectin mainly in parallel clumps between cells. Cells expressing both the SV40 large T antigen and the EJ ras oncogene, at high cell density, displayed networks of fibronectin arranged in matrix-like patterns between cells. The malignant **cell line** examined, sarcoma cells, also exhibited fibronectin networks between cells. Cell density affected fibronectin deposition in **endometrial** stromal cells expressing the EJ ras oncogene. At low density, cells expressing the SV40 large T antigen and the EJ ras oncogene displayed diffuse fibronectin patterns and, at high density, these cells formed colonies with networks of fibronectin between cells.

L8 ANSWER 13 OF 16 MEDLINE DUPLICATE 4

L8 ANSWER 11 OF 16 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 92347457 MEDLINE
DOCUMENT NUMBER: 92347457 PubMed ID: 1322312
TITLE: Differential effects of dioctanoylglycerol on fibronectin localization in normal, partially transformed, and malignant human **endometrial** stromal cells.
AUTHOR: **Carter C A**; Albright C D; Kaufman D G
CORPORATE SOURCE: Experimental Toxicology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709.
CONTRACT NUMBER: CA31733 (NCI)
ES07017 (NIEHS)
SOURCE: EXPERIMENTAL CELL RESEARCH, (1992 Aug) 201 (2) 262-72.
Journal code: EPB; 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920911
Last Updated on STN: 19970203
Entered Medline: 19920903

AB In this study, we describe the effects of direct activation of PKC by dioctanoylglycerol (DiC8) on cellular morphology and the localization of fibronectin (Fn) in normal, oncogene-transfected, and malignant human **endometrial** stromal cells. We questioned whether DiC8, an endogenous specific activator of PKC, would function as a second oncogene in partially transformed human **endometrial** stromal cells (HESC). Cells utilized were (1) normal HESC, (2) HESC transfected with a plasmid containing an origin-defective temperature-sensitive SV40 large T antigen alone or (3) in combination with an EJ ras oncogene, and (4) an **endometrial** sarcoma **cell line** (S7). Cell cultures were treated for 1 h with sn-dioctanoylglycerol (DiC8) and stained with a monoclonal fluorescein-labeled anti-Fn antibody. In normal HESC, DiC8 induced cell rounding and caused Fn localization to revert from the perinuclear region to the cell periphery. All experiments in this investigation were performed when cells were maintained at the permissive temperature for SV40 large T antigen function. In HESC expressing the SV40 large T antigen alone, Fn was localized to the perinuclear region and also occurred as parallel strands between cells. When these cells were treated with DiC8, Fn localization changed to intense punctate regions at the cell periphery or to matrix-like patterns between cells. Also, in these cells, DiC8 induced greater detachment of cells from the substrate than from other cells, resulting in an apparent piling up of cells. Control and treated SV40/EJ ras cells and **uterine** sarcoma cells expressed Fn in a matrix-like pattern between cells. The rounded cellular morphology of treated HESC and treated cells expressing SV40 resembled the morphology of control or treated SV40/EJ ras cells and **uterine** sarcoma cells. Thus, treated cells expressing the SV40 large T antigen resembled the SV40/EJ ras cells and **uterine** sarcoma cells with respect to Fn localization and cellular morphology. DiC8 did not appear to further

transform HESC expressing SV40 and EJ ras. However, with regard to cell shape and Fn localization, our results suggest that DiC8 may function as a second oncogene in the signal transduction pathway, in cells expressing SV40 alone. It appears that, with regard to Fn localization, DiC8 may alter signal transduction analogously to that caused by the activated Ha-ras oncogene in HESC expressing the SV40 large T antigen.

L8 ANSWER 10 OF 16 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 94030588 MEDLINE
DOCUMENT NUMBER: 94030588 PubMed ID: 7692874
TITLE: Localization of tenascin in **uterine** sarcomas and partially transformed **endometrial** stromal cells.
AUTHOR: Vollmer G; Lightner V A; **Carter C A**; Siegal G P; Erickson H P; Knuppen R; Kaufman D G
CORPORATE SOURCE: Institut fur Biochemische Endokrinologie, Medizinische Universitat, Lubeck, FRG.
CONTRACT NUMBER: AR 38479 (NIAMS)
CA 31733 (NCI)
ES 07017 (NIEHS)
+
SOURCE: PATHOBIOLOGY, (1993) 61 (2) 67-76.
Journal code: AF6; 9007504. ISSN: 1015-2008.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19970203
Entered Medline: 19931217

AB Normal mesenchymal cells within developing embryonic organs and transformed stromal cells in organs undergoing spontaneous carcinogenesis have the capacity for normal or altered expression of the extracellular matrix glycoprotein tenascin (Tn). Mesenchymal cell constituents of normal adult organs show only a very limited tendency to deposit Tn in their extracellular matrix. In the present study, we investigated whether malignant human mesenchymal cells derived from **uterine** sarcomas or normal human **endometrial** stromal cells partially transformed via transfection with selected oncogenes have the capacity to produce and deposit Tn. We reached the following conclusions: (1) compared with normal **endometrial** tissues, **uterine** sarcomas show heterogeneous, but increased, immunoreactive staining patterns exclusively within the extracellular compartment, regardless of the histologic subtype of the tumor; (2) in vitro, all normal and transfected stromal cells and **cell lines** examined secreted Tn into the tissue culture medium; (3) this secretory ability was not translated into morphologic uniformity, since immunoreactivity detected by confocal laser scanning microscopy was observed in only selected cell populations; (4) also, the deposition and the incorporation of Tn depended upon the density of transfected cells, and (5) double-staining experiments revealed that Tn could always be localized in close proximity to fibronectin. In summary, the production of Tn is increased in most cases of human **uterine** sarcoma. The capacity of stromal cells to deposit Tn in a matrix-like structure in vitro, rather than increase production of Tn, is correlated with the degree of neoplastic progression.

L8 ANSWER 11 OF 16 MEDLINE DUPLICATE 2

L14: Entry 15 of 54 File: USPT Jun 6, 2000

DOCUMENT-IDENTIFIER: US 6071691 A
TITLE: Materials and methods for modulating differentiation

DATE FILED (1):
19980427

Brief Summary Paragraph Right (1):
Rhabdomyosarcomas are highly malignant tumors composed of primitive muscle cells (stem cells) having a low propensity to differentiate. Cells of this type are grouped by histologic and cytogenetic criteria as either embryonal or alveolar rhabdomyosarcomas. The two types are distinguished by detection in embryonal rhabdomyosarcomas of a loss of heterozygosity on the short arm of chromosome 11 encompassing 11p15.5 [Mitchell et al, Oncogene, 6:89-92 (1991)] and in alveolar rhabdomyosarcomas, of a balanced translocation between chromosomes 2 and 13, t(2:13)(q35;q14) [Barr et al., Nat. Genet., 3:113-117 (1993)]. Loss of heterozygosity at 11p15.5 is also

Brief Summary Paragraph Right (3):
In tumor cells, expression of the muscle differentiation factor MyoD [Weintraub, H., Cell, 75:1241-1244 (1993)] has been shown to be a highly sensitive marker for classifying sarcomas as rhabdomyosarcomas [Dias et al., Am. J. Pathol., 137:1283-1291 (1990); Scrable et al., Proc. Natl. Acad. Sci., USA, 87:2182-2186 (1990)]. MyoD is a member of a large family of transcription factors that belong to the basic-helix-loop-helix (BHLH) family known to control cell fate determination and stem cell function. While MyoD is associated with myoblast differentiation, related proteins determine the fate of other primitive cell types. For example, SCL controls Hematopoietic stem cell differentiation [Porcher, et al., Cell 86:47-57 (1996)] and neurogenic stem cell differentiation is controlled by the BHLH proteins MASH, neurogenin, and neuro D [Reviewed in Morrison et al., Cell 88:287-298 (1997) and Andersen, FASEB J., 8:707-713 (1994)]. Similarly, liver stem cell differentiation is regulated by a combination of transcription factors including NF-.kappa.B, Stat3, and C/EBP [Taub, FASEB J. 10:413-427 (1996)]. Conversely, expression of transforming oncogenes inhibits cellular differentiation in several different cell lineages [Holtzer et al., Proc. Natl. Acad. Sci. USA, 72:4051-4055 (1975); Lassar et al., Cell, 58:659-667 (1989)]. In muscle cells, for example, expression of oncogenic tyrosine kinases (v-src and v-fps), growth factor receptors (v-erbB), nuclear oncogenes (v-myc, c-myc, v-erbA, E1A, and MDM2), and the activated form of signal transducing G proteins (H-ras and N-ras) can inhibit terminal differentiation to varying degrees [Fiszman and Fuchs, Nature, 254:429-431 (1975); Holtzer et al., Proc. Natl. Acad. Sci. USA, 72:4051-4055 (1975); Fiddler et al., Mol. Cell Biol. 16:5048-5057 (1996)]. The paradox that MyoD, shown to induce muscle differentiation in a wide variety of primary cells and transformed cell lines [Weintraub et al., Proc. Natl. Acad Sci., 86:5434-5438 (1989)], serves as a hallmark for identification of a particular tumor type may be resolved by the possibility that MyoD appears to be non-functional in the neoplastic cells.

Brief Summary Paragraph Right (4):
In rhabdomyosarcomas, abnormalities in protein expression have been reported, including for example, p53 and ras expression [Hiti et al., Mol. Cell Biol., 9:4722-4730 (1989); Dias et al., Am. J. Pathol., 137:1283-1291 (1990), Loh et al. Proc. Natl. Acad Sci. USA, 89:1755-1759 (1992)], however, the loci involved in the 11p loss of heterozygosity have not been identified. It is clear, however, that MyoD expression is unaffected [Scrable et al, Proc. Natl. Acad Sci., USA, 87:2182-2186 (1990)]. Chromosome transfer experiments wherein a normal chromosome 11 was introduced into rhabdomyosarcoma cells resulted in inhibition of cell growth and tumor formation in nude mice but had no effect on myogenic differentiation [Loh et al., Proc. Natl. Acad. Sci. USA,

89:1755-1759 (1992)]. Thus, the loss of the chromosome 11 locus was shown not to be responsible for the lack of differentiation in embryonal rhabdomyosarcomas.

Brief Summary Paragraph Right (6):
In addition to the above chromosomal abnormalities, chromosome 3q alterations have been found to occur frequently in rhabdomyosarcomas. Previous studies have shown that gain of 3q was present in two out often embryonal rhabdomyosarcomas [Weber-Hall et al., Cancer Res., 56:3220-3224 (1996)]. In addition, gain of 3q has been observed at high frequency in several other types of tumors, including, for example, 52% of prostate tumors [Cher et al., Cancer Res., 56:3091-3102 (1996)], ten out of thirteen small cell lung carcinomas [Ried et al., Cancer Res., 54:1801-1806 (1994)], ten out of thirteen head and neck squamous cell carcinomas [Speicher et al., Cancer Res., 55: 1010-1013 (1995)], and nine out of ten cervical carcinomas [Heselmeyer et al., Proc. Natl. Acad. Sci. USA, 93:479-484 (1996)]. Furthermore, the gain of chromosome 3q by isochromosome formation in HPV16-infected cells defines the transition from severe dysplasia to invasive carcinoma of the uterine cervix [Heselmeyer et al., Proc. Natl. Acad. Sci. USA, 93:479-484 (1996)].

Brief Summary Paragraph Right (27):
The invention further provides methods to promote differentiation of a differentiation-inhibited cell comprising the step of contacting the cell with a compound that inhibits transcription of a polynucleotide encoding a cell cycle checkpoint protein. Alternatively, the invention embraces methods for promoting differentiation of a differentiation-inhibited cell comprising the step of introducing into the cell a polynucleotide encoding a mutated cell cycle checkpoint protein; said polynucleotide providing a dominant/negative phenotype in the cell. In both aspects, the preferred cell type is a tumor cell. A preferred tumor cell is selected from the group consisting of a rhabdomyosarcoma cell, a prostate tumor cell, a small cell lung carcinoma cell, a head squamous cell carcinoma cell, a neck squamous cell carcinoma cell, a cervical carcinoma cell, and a uterine cervix carcinoma cell.

Detailed Description Paragraph Right (5):
aneuploid nature of the cell line supports this possibility. Second, it is possible that the Rh30 cells have a recessive phenotype but a fraction of the cells in the Rh30 population have lost to capacity to express MyoD and myogenin. If this explanation were true, the MyoD and myogenin negative cells would no longer be able to induce myogenesis when fused to 10T1/2 cells. This cell line was therefore chosen to examine the inability of MyoD to induce differentiation in rhabdosarcoma cells.

Detailed Description Paragraph Right (19):
Results indicated that the parental C2C12 cells, as well as C2C12 microcell hybrids containing normal chromosome 3, displayed relatively stable tetraploid karyotypes with the majority of cells containing 76-85 chromosomes. In contrast, the microcell hybrids, C2(Rh30)-2, C2(Rh30)-21, C2(R302)-3, that retained i(3q) displayed aneuploid karyotypes with the majority of metaphase spreads containing greater than 156 chromosomes. Furthermore, metaphase spreads with greater than 300 chromosomes were observed in all three of the i(3q)-containing hybrids analyzed. These results indicated that introduction of the i(3q) into C2C12 cells caused the cells to become aneuploid, while transfer of normal chromosome 3 did not.

Detailed Description Paragraph Right (34):
Two clones, C2ATR-1 and C2ATR-5, were found to express reduced levels of MyoD, myogenin and MLC1/3 mRNA as compared to parental C2C12 cells. Thus, the C2C12 cells transfected with the ATR expression vector have a phenotype similar to the i(3q) hybrids with respect to muscle differentiation. Chromosome counts on the two clones indicated the two contained aneuploid karyotypes similar to the i(3q) containing hybrids. Chromosome counts on C2C12 clones transfected with empty expression vector (C2cDNA1 and 2), all retained a stable tetraploid karyotype. Immunostaining C2ATR-1 and C2ATR-5 with the .beta. and .gamma. tubulin antibodies showed centrosome amplification leading to supernumerary spindles.

Detailed Description Paragraph Right (35):
Forced expression of ATR therefore resulted in a phenocopy of the i(3q) containing hybrids, and that duplication of ATR by isochromosome formation caused loss of myogenic differentiation, abnormal centrosome amplification, and aneuploidy in the rhabdomyosarcoma cell line Rh30.

Detailed Description Paragraph Right (43):
To determine whether the CHK1 transfected clones contain cell-cycle abnormalities

similar to the i(3q) hybrids, chromosome counts on two ATR stable lines, C2CHK-3 and C2CHK-4 were conducted. Similar to the i(3q) containing hybrids, these two clones contain aneuploid karyotypes. Immunostaining C2CHK-3 with the .gamma. and .beta. tubulin antibodies showed centrosome amplification leading to supernumerary spindles.

Other Reference Publication (26):
Heselmeyer, et al., "Gain of chromosome 3q defines the transition from severe dysplasia to invasive carcinoma of the uterine cervix," Proc.Nat'l.Acad.Sci.(USA) 93:479-484 (1996).

L14: Entry 22 of 54 File: USPT Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6007985 A
TITLE: Macromolecule delivery method and composition

DATE FILED (1):
19941202

Brief Summary Paragraph Right (13):
Physicians often base a diagnosis of cancer on morphological alterations observed in a tissue biopsy or exfoliated cells. Once a tumor has been detected, it is common practice in surgical pathology to "grade" the tumor. Tumor grading provides an estimate of the aggressiveness or biological behavior of the tumor, and involves identification of morphological changes correlating tumor behavior. One parameter used for the grading of certain types of tumors, such as uterine leiomyosarcoma, neuroblastoma, breast carcinoma, and others, is the mitotic activity of the tumor. The mitotic activity, or mitotic index, provides an estimate of the growth rate of the tumor. The pathologist examines microscopic sections of the tumor, stained with conventional cell stains such as hematoxylin and eosin, and counts the number of mitotic figures per high powered field. This procedure can be tedious and is subject to errors related to inadequate sampling and misinterpretation.

Brief Summary Paragraph Right (19):
Cell cycle analysis of individual cell nuclei may be accomplished by extracting nuclei from fixed tissues that have been embedded in paraffin blocks, and staining the DNA with a fluorescent dye, such as propidium iodide. The distribution of G1, S and G2 phase nuclei are roughly determined by the relative fluorescence intensity of the individual nuclei passing through the flow cytometer. This approach has been beneficial in that it provides prognostically valuable information, such as the fraction of cells in G1 or G2/M or the presence of aneuploidy, but has significant limitations. First, the extraction, staining and flow cytometric analysis of nuclei is technically demanding. Second, some variation exists in the integration of DNA dye into the nucleus due to differences in chromatin density. In addition, the S-phase fraction of the cell population cannot be measured directly by flow cytometric analysis. Therefore, the S-phase fraction must be calculated using a sophisticated computer analysis involving complex mathematical algorithms.

Drawing Description Paragraph Right (3):
FIG. 1B shows expression of Pol II LS in an uninduced, undifferentiated cell.

Detailed Description Paragraph Right (26):
Anti-Pol II LS antibodies can be used to detect and distinguish proliferating cells from non-proliferating cells and to distinguish malignant non-dividing cells from normal non-dividing cells in a biological sample taken from a human patient or research animal. The biological sample can be a tissue biopsy, cells in a biological fluid such as a peripheral blood smear, and a cytological specimen such as a cervical smear. In addition, because the antibodies described herein stain both fresh tissues and tissues fixed in formalin and embedded in paraffin, the biological sample can be fresh or preserved. Therefore, anti-Pol II LS antibodies can be used as diagnostic agents for the diagnosis of a proliferative disease such as cancer, relapse of a proliferative disease such as neoplasia, or to assess the effectiveness of a particular therapy, such as chemotherapy or radiation therapy for treatment of a proliferative disease. In particular, anti-Pol II LS antibodies can be used for early diagnosis of rapidly dividing tumors, such as seminoma and acute leukemia. Furthermore, anti-Pol II LS antibodies can be used for endometrial dating to allow an easy, quick assessment of a proliferative endometrial cell sample exfoliated from the endometrial lining of the uterus and for analysis of early "precursor" lesions, such as atypical hyperplasias or

fibrocystic changes in breast tissue biopsies, or atypical hyperplasia of the endometrial glands for identification of those individuals at greatest risk for the development of cancer.

Detailed Description Paragraph Right (66):
Normal and malignant breast ductal cells were stained with the peroxidase-labelled anti-Pol II LS monoclonal antibody H5. Cytoplasmic Pol II LS was undetectable in normal, non-dividing breast ductal cells. However, in malignant, non-dividing ductal cells marked cytoplasmic Pol II LS immunoreactivity was observed. Similar results were obtained by immunoperoxidase staining of uterine leiomyosarcomas, germ cell neoplasms and other carcinomas. The abnormal nucleocytoplasmic compartmentalization of Pol II LS is a feature of many types of malignant cells.

L14: Entry 35 of 54 File: USPT Dec 1, 1998

DOCUMENT-IDENTIFIER: US 5843649 A
TITLE: Method of identifying clonal cell samples using heteroduplex generators

DATE FILED (1):
19950301

Brief Summary Paragraph Right (2):
The histologic distinction between malignant and pseudo-malignant cellular proliferative processes may be difficult. For example, the distinction between endometrial hyperplasia with atypia and adenocarcinoma relies on subtle qualitative and quantitative changes, and the two often cannot be differentiated with absolute certainty. More objective data to support the diagnosis of a benign versus malignant proliferative process could be of great benefit in determination of prognosis and in guiding subsequent clinical management.

Brief Summary Paragraph Right (3):
A wide variety of approaches including analysis of karyotypic abnormalities, gene rearrangements, oncogene and anti-oncogene mutations, and loss of heterozygosity have been utilized for the investigation of clonal composition in neoplastic tissues. Each of these methods, however, are potentially informative in only a subset of cases, typically including moderately and poorly differentiated tumors which are readily diagnosed as malignant by microscopic examination.

Drawing Description Paragraph Right (3):
FIGS. 3A and 3B show a clonal analysis of a well differentiated endometrial adenocarcinoma representative case (case B). In FIG. 3A, note the back-to-back glands with modest nuclear atypia (H&E). FIG. 3B shows PCR amplification of PGK-1 and analysis by HG. Lanes 1, 3, 5 =control tissue (myometrium); lanes 2, 4, 6=tumor. Arrow indicates migration of amplification products at apparent molecular weight of 548 bp. Hybridization with the HG resulted in generation of four discrete heteroduplex bands (lanes 3, 4) Treatment of DNA with HpaII prior to amplification resulted in loss of two of the four heteroduplex bands from tumor (lane 6), but not control (lane 5), consistent with the clonal composition of the tumor. M, 100 bp ladder.

Drawing Description Paragraph Right (5):
FIGS. 5A and 5B show a clonal analysis of a poorly differentiated endometrioid adenocarcinoma (case C). In FIG. 5A, note the marked nuclear pleomorphism and abnormal mitotic figures (H&E). FIG. 5B shows PCR amplification of PGK-1 and analysis by HG. Lanes 1, 3, 5=control tissue (focally necrotic granulation tissue); lanes 2, 4, 6=tumor. Arrow indicates migration of amplification products at apparent molecular weight 548 bp. Hybridization with the HG resulted in generation of multiple heteroduplex bands of dissimilar intensity (lanes 3, 4). Treatment of DNA with HpaII prior to amplification resulted in anomalous patterns of reduction of heteroduplex bands (lanes 5, 6), suggestive of the presence of aneuploid cells in tissue from both control and tumor. M, 100 bp ladder. As shown in this figure, HG analysis is less valuable for poorly differentiated samples relative to the results seen above for well differentiated samples. This is due to the fact that poorly differentiated samples are indicative of extensively developed malignancy. Poorly differentiated malignant cells often degrade genetically. As shown in Table 4, cells for this sample had 0 or 1 X chromosome making the technique that is the present invention less effective. However, since poorly differentiated samples do not present diagnostic problems associated with well differentiated samples, these results do not diminish the overall usefulness of the invention.

Detailed Description Paragraph Right (38):

Examples include any disease where a lesion with well differentiated cells must be analyzed to determine whether the tissue sample is a neoplasm or a pseudoneoplastic or hyperplastic process. By testing to determine if the cells of the tissue sample are a clonal population or a mosaic population, a determination can be made whether the sample is a neoplasm or a pseudoneoplastic or hyperplastic process, and a therapeutic course of action can be undertaken based upon the diagnosis made using the information obtained using the invention. The present invention provides methods, reagents and kits for differential diagnosis in cases where neoplastic lesions must be distinguished from pseudo-neoplastic or hyperplastic processes. A list of applications of the methods of the invention is included in Table 2 which describes the pseudoneoplastic or hyperplastic conditions versus the neoplastic conditions which can be distinguished using clonality analysis according to the invention. In a preferred embodiment, lesions in the uterus which may be either well differentiated endometrial adenocarcinoma or endometrial hyperplasia with atypia are common examples of situations where a sample from a female may consist of clonal neoplastic cells or pseudoneoplastic cells and be distinguished by clonal analysis.

Detailed Description Paragraph Right (50):
Thirty-seven patients diagnosed with uterine endometrioid adenocarcinoma over an eight year period (1984-1992) were identified through the Colorado Central Cancer Registry. Tumors were classified and graded using standard diagnostic criteria. The patients ranged in age from 40 to 80 years at the time of diagnosis (mean age 63.5 years). Hematoxylin and eosin stained tissue sections from the formalin-fixed, paraffin-embedded tissue blocks were examined to identify areas where the lesional cells comprised greater than 50% of the total cell population. Microdissection of lesional cells was performed on 4 .mu.m thick hematoxylin and eosin stained sections, under 50% (v/v) aqueous glycerol, using a 28 g hypodermic needle (Becton Dickinson, Franklin Lakes, N.J.) attached to a Leitz (Wetzlar, Germany) micromanipulator and a hand-held 2.0 .mu.l glass pipette (Drummond Scientific, Broomwall, Pa.) with vacuum control. Quantitative assessment by microscopic examination of 100 cells showed that greater than 90% of cells collected from lesional tissue consisted of the intended target epithelial population. DNA of lesional cells and control tissue (benign myometrium) was deparaffinized and the DNA was extracted by Proteinase K digestion, according to standard protocols. Following digestion, the DNAs were extracted with phenol, ethanol precipitated, redissolved in H.sub.2 O, and the DNA content was measured spectrophotometrically (Beckman DU-50, Fullerton, Calif.).

Detailed Description Paragraph Right (63):
A total of 37 cases originally diagnosed as endometrioid adenocarcinoma were entered into the study. PCR was successful in amplification of the PGK-1 target in 36/37 cases. HG analysis of 36 cases demonstrated heterozygosity in 12 cases (33.3%) . These same 12 cases were also shown to be heterozygous by BstXI RFLP analysis of the PGK-1 amplification product. No additional polymorphisms were identified by the HG in BstXI RFLP negative cases. Amplified product for clonality analysis was obtained from both control and lesional tissues in 10 of 12 cases (Table 3), including 3 cases of well differentiated carcinoma, 5 cases of moderately differentiated carcinoma, and 2 cases of poorly differentiated carcinoma (Table 3).

Detailed Description Paragraph Right (64):
HG analysis of PGK-1 PCR amplification products from HpaII treated genomic DNA demonstrated clonal composition of cells in 7 of the 10 informative cases (FIG. 3). Clonal cases included 1 case of well differentiated carcinoma, 5 cases of moderately differentiated carcinoma, and 1 case of poorly differentiated carcinoma. HG analysis of cases G and I demonstrated polyclonal composition of the lesional tissue (FIG. 4). Both polyclonal cases were diagnosed as well differentiated carcinomas without evidence of myometrial invasion.

Detailed Description Paragraph Right (65):
HG analysis in case C suggested an anomalous pattern of X-chromosome inactivation in both tumor and control tissue (FIG. 5). Among the 10 informative cases, case C was the only one which has shown evidence of metastatic dissemination. Review of the histopathologic features of this poorly differentiated carcinoma revealed extreme nuclear pleomorphism and numerous abnormal mitotic figures, strongly suggestive of aneuploid X-chromosome content. The control in this case showed myometrium with focally necrotic granulation tissue and scattered highly atypical cells, suspicious for infiltrative tumor cells. FISH analysis of case C, using an alpha-satellite probe for the X-chromosome (DXZ1), demonstrated hypodiploid X-chromosome content in a high proportion of both tumor cells and in atypical cells present in granulation tissue which was used as the control tissue (Table 4).

Detailed Description Paragraph Right (70):
The differential diagnosis between atypical hyperplasia and well differentiated adenocarcinoma of the endometrium is often difficult due to subtle qualitative and quantitative features which are used for the distinction between these entities. In terms of impact on the patient, it is imperative to be as accurate as possible in the diagnosis of carcinoma. In the current study, 2 of 3 cases diagnosed as well differentiated endometrioid adenocarcinoma were found to be composed of polyclonal cell populations. The 2 polygonal cases showed no evidence of myometrial invasion, raising the possibility that they could represent pseudoneoplastic proliferative processes. It is also possible that these cases represent technical failures of the PCR-based clonality assay. Since our mixing study indicated that the method can detect the presence of a clonal cell population in a background of up to 40% normal cells, however, it seems unlikely that these results were caused by contamination of the sample with DNA from non-neoplastic components of the tissue. While large studies of clonality correlating results with clinical outcome assessment, will be required, these preliminary results suggest the potential of clonality analysis as an aid for diagnostic purposes.

Detailed Description Paragraph Table (2):
TABLE 2 Pseudoneoplastic or hyperplastic conditions versus neoplastic conditions must be distinguished from each other in diagnosing female individuals with lesions. A list of applications of the methods of the invention is included in Appendix B which describes the conditions which can be distinguished from each other using clonality analysis according to the invention. 1. Atypical nevus vs. melanoma 2. Actinic keratosis vs. squamous cell carcinoma 3. squamous hyperplasia of oral mucosa vs. squamous cell carcinoma 4. Verrucous hyperplasia vs. verrucous carcinoma 5. Pituitary hyperplasia vs. pituitary adenoma 6. Parathyroid hyperplasia vs. parathyroid adenoma 7. Adenomatoid change in colloid goiter vs. follicular carcinoma of thyroid 8. Cervical dysplasia vs. cervical carcinoma in situ 9. Reactive atypia or glandular dysplasia vs. colonic adenocarcinoma 10. Granulation tissue vs. carcinoma 11. Nodular fascitis vs. sarcoma 12. Endometrial hyperplasia vs. endometrial adenocarcinoma 13. Metastatic tumors vs. multiple independent primary tumors. 14. Adrenal cortical hyperplasia vs. adrenal cortical adenoma or adenocarcinoma 15. Endosalpingrosis vs. metastatic papillary seroces adenocarcinoma 16. Focal nodular hyperplasia of liver vs. hepatic adenoma or hepatocellular carcinoma 17. Chronic pancreatitis with reactive atypia vs. pancreatic adenocarcinoma 18. Cholangiocarcinoma vs. reactive atypia of ductal epithelium 19. Atypical ductal hyperplasia vs. ductal carcinoma in situ of breast 20. Atypical lobular hyperplasia vs. lobular carcinoma in situ

Detailed Description Paragraph Table (3):
TABLE 3
Analysis of clonality in endometrial hyperplasia and carcinoma Year Myometrial Metastatic Hpa II Case collected Tissue diagnosis invasion dissemination.sup.a monoclonal.sup.c
A 1989 Uterus, endometrioid adenocarcinoma (grade - - + II/III) Uterus, benign myometrium - B 1992 Uterus, endometrioid adenocarcinoma (grade I/III) + - + Uterus, benign myometrium - C 1984 Uterus, endometrioid adenocarcinoma (grade + + An..sup.c III/III) Uterus, myometrium with focally necrotic An..sup.c granulation tissue D 1990 Uterus, endometrioid adenocarcinoma (Grade + - + II/III) Uterus, benign myometrium - E 1990 Uterus, adenosquamous carcinoma (grade III/III) + - + Uterus, benign myometrium - F 1989 Uterus, endometrioid adenocarcinoma (grade + - + II/III) Uterus, benign myometrium - G 1992 Uterus, endometrioid adenocarcinoma (grade I/III) - - - Uterus, benign myometrium - H 1986 Uterus, endometrioid adenocarcinoma (grade + - + II/III) Uterus, benign myometrium - I 1990 Uterus, endometrioid adenocarcinoma (grade I/III) - - - Uterus, benign myometrium - J 1990 Uterus, endometrioid adenocarcinoma (grade + - + II/III) Uterus, benign myometrium -
.sup.a Metastatic dissemination denotes cases with known local or distant metastases from the time of initial diagnosis through conclusion of the study (four of 94), as determined by case records of the Colorado Central Cancer Registry. .sup.b Hpa II monoclonal denotes cases from which HG analysis of PCR products from Hpa IItreated genomic DNA showed marked attenuation or loss of signal for two of four heteroduplex bands. .sup.c An. denotes cases from which PCR produced an anomalous pattern of PGK1 amplification, precluding analysis of clonality.

Detailed Description Paragraph Table (4):

TABLE 4 FISH analysis of X-chromosome content in poorly differentiated endometrioid adenocarcinoma (case C) Hybridization signals/nucleus (% cells) Tissue diagnosis 0 1 2 3

Uterus endometrioid 5 55 38.5 1.5 adenocarcinoma (grade III/III) Uterus, focally necrotic 10 56 33 1 granulation tissue

Other Reference Publication (8):

Mutter, G. et al, "A Polymerase Chain Reaction Assay for Non-Random X Chromosome Inactivation Identifies Monoclonal Endometrial Cancers", Am. J. of Pathology 1995, 146(2), 501-508.

CLAIMS:

2. The method of claim 1 wherein said neoplasm is adenocarcinoma and said pseudoneoplastic or hyperplastic process is endometrial hyperplasia with atypia.

WEST

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L17: Entry 88 of 139 File: DWPI Oct 15, 1999

DERWENT-ACC-NO: 2000-169433
DERWENT-WEEK: 200110

TITLE: Human uterine neck cancer cell line - NoAbstract

INVENTOR: KU, J L; PARK, J ; KOO, J R ; PARK, J G

PATENT-ASSIGNEE: KU J L (KUJLI), PARK J (PARKI), KOO J R (KOOJI), PARK J G (PARKI)

PRIORITY-DATA: 1997KR-0032340 (July 11, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
KR 225491 B1	October 15, 1999		000	C12N005/22
KR 99009815 A	February 5, 1999		000	C12N005/22

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
KR 225491B1	July 11, 1997	1997KR-0032340	
KR 99009815A	July 11, 1997	1997KR-0032340	

INT-CL (IPC): C12 N 5/22

CHOSEN-DRAWING: Dwg.1/6

DERWENT-CLASS: B04 D16
CPI-CODES: B04-F02; D05-H14B2; E10-E03; E11-Q03J;

WEST

Generate Collection Print

L17: Entry 72 of 139 File: DWPI Dec 15, 2000

DERWENT-ACC-NO: 2000-466216
DERWENT-WEEK: 200107

TITLE: New endometrial stroma cell line infected with hepatitis virus C - for producing virus and vaccines and for antiviral screening

INVENTOR: DORNER, F; EDER, G ; PAVLOVA, B ; SCHAFF, Z

PATENT-ASSIGNEE: IMMUNO AG (IMMO)

PRIORITY-DATA: 1998AT-0001098 (June 24, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AT 407256 B	December 15, 2000		000	C12N005/00
AT 9801098 A	June 15, 2000		020	C12N005/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AT 407256B	June 24, 1998	1998AT-0001098	
AT 407256B		AT 9801098	Previous Publ.
AT 9801098A	June 24, 1998	1998AT-0001098	

INT-CL (IPC): A61 K 39/29; C12 N 5/00; C12 N 7/02; G01 N 33/53

ABSTRACTED-PUB-NO: AT 9801098A
BASIC-ABSTRACT:

NOVELTY - An endometrial stroma cell line (A) derived from uterine mucosal tissue and infected with hepatitis C virus (HCV), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (a) a composition for detecting anti-HCV antibodies (Ab) comprising (A), reagents for detecting an immune reaction, and HCV-positive and -negative plasmas as controls; (b) long-term production of HCV by culturing (A), optionally monitoring viral replication by reverse transcription polymerase chain reaction (RT-PCR), and recovering virus from the culture supernatant; (c) production of HCV vaccine by isolating HCV, as in (b), production of a high-titer concentrate and formulation of this to vaccine; (d) screening for agents (I) that inhibit replication of HCV by incubating (A) with test compounds and detecting any inhibition of viral replication by RT-PCR; and (e) detecting Ab by treating (A) with a sample suspected of containing Ab and detecting formation of an antigen/Ab complex.

BIOLOGY - Preferred Cell Lines: These are (i) derived from uterine tissue of a subject infected with a flavi-, herpes-, orthomyxo-, papilloma- or parvo-virus (specifically HCV), particularly after establishment of the cell line. Both E4 and F13 are isolated from chimpanzees.

Preferred Composition: The composition of (a) has (A) immobilized on a carrier.

Preferred Process: Method (b) may be any conventional immunoassay, e.g. an enzyme-linked immunosorbent assay.

ACTIVITY - Virucide.

MECHANISM OF ACTION - None given.

USE - (A) are used (i) for production of flavi-, herpes-, orthomyxo-, papilloma- or parvo-viruses, especially HCV for preparation of vaccines; (ii) to detect anti-HCV antibodies; and (iii) for identifying agents, potential antivirals, that inhibit replication of HCV.

ADVANTAGE - (A), which are spontaneously immortalized, permit long-term, continuous production of viruses, e.g. for at least 14 months.

EXAMPLE - Uterine mucosal tissues were isolated, during the proliferative phase of the menstrual cycle, from two chimpanzees, one (E4) chronically infected with hepatitis C virus (HCV) and the other (F13) not infected. The tissues were comminuted mechanically then separated on a Ficoll- Hypaque (RTM) gradient at density 1.077 g/ml. Cells from the upper phase of the gradient were collected, washed then grown in serum-containing medium. Once cells had reached 80 % confluence, they were mechanically removed and passaged. From E4, non-adherent cells were eliminated by medium exchange and the adherent cells formed a uniform, fibroblastic adhesive layer with doubling time 14 - 21 days. These cells were grown in continuous culture, without addition of growth factors, for at least 14 months, although the rate of proliferation did decline slightly after 7 months. Further passaging produced the cell line E4. The supernatants from this cell line were positive, by reverse transcription polymerase chain reaction, for HCV RNA, at times beyond about 5 months (passage 7), with viral copy number a maximum between months 7 and 14 (passages 10 - 14). These supernatants also showed a reduction in Fas activity, in parallel with the increase in HCV RNA content, indicative of reduced apoptotic activity.

ABSTRACTED-PUB-NO: AT 9801098A
EQUIVALENT-ABSTRACTS:

CHOSEN-DRAWING: Dwg.0/1

DERWENT-CLASS: B04 D16 S03
CPI-CODES: B04-F0200E; B04-F11; B04-G08; B11-C07A4; B11-C08E3; B11-C08E5; B12-K04E; B12-K04F; B14-S11A; D05-H06; D05-H07; D05-H08; D05-H09; D05-H10; D05-H14B2;
EPI-CODES: S03-E14H4;